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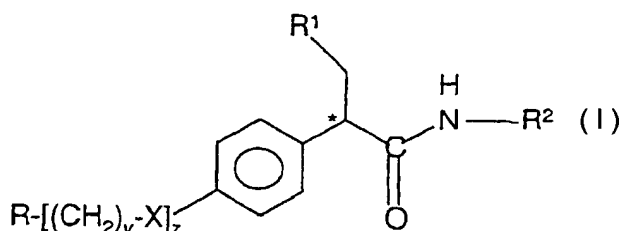
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(54) Title: SUBSTITUTED PHENYLACETAMIDES AND THEIR USE AS GLUCOKINASE ACTIVATORS



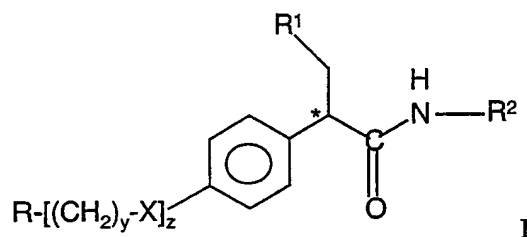
(57) Abstract: Compounds of formula (I) wherein X is oxygen or sulfonyl, R is a ring, R¹ is cycloalkyl, y and z are 0 or 1, and R² is -CO-NHR³ or a heteroaromatic ring having a ring nitrogen atom adjacent to the connecting ring carbon atom, are active as glucokinase activators to increase insulin secretion, which makes them useful for treating type II diabetes.

SUBSTITUTED PHENYLACETAMIDES AND THEIR USE AS GLUCOKINASE ACTIVATORS

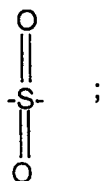
Glucokinase (GK) is one of four hexokinases found in mammals [Colowick, S.P., in *The Enzymes*, Vol. 9 (P. Boyer, ed.) Academic Press, New York, NY, pages 1-48, 1973]. The hexokinases catalyze the first step in the metabolism of glucose, i.e., the conversion of glucose to glucose-6-phosphate. Glucokinase has a limited cellular
5 distribution, being found principally in pancreatic β -cells and liver parenchymal cells. In addition, GK is a rate-controlling enzyme for glucose metabolism in these two cell types that are known to play critical roles in whole-body glucose homeostasis [Chipkin, S.R., Kelly, K.L., and Ruderman, N.B. in *Joslin's Diabetes* (C.R. Khan and G.C. Wier, eds.), Lea and Febiger, Philadelphia, PA, pages 97-115, 1994]. The concentration of glucose at
10 which GK demonstrates half-maximal activity is approximately 8 mM. The other three hexokinases are saturated with glucose at much lower concentrations (<1 mM). Therefore, the flux of glucose through the GK pathway rises as the concentration of glucose in the blood increases from fasting (5 mM) to postprandial (≈ 10 -15 mM) levels following a carbohydrate-containing meal [Printz, R.G., Magnuson, M.A., and Granner, D.K. in *Ann.*
15 *Rev. Nutrition* Vol. 13 (R.E. Olson, D.M. Bier, and D.B. McCormick, eds.), Annual Review, Inc., Palo Alto, CA, pages 463-496, 1993]. These findings contributed over a decade ago to the hypothesis that GK functions as a glucose sensor in β -cells and hepatocytes (Meglasson, M.D. and Matschinsky, F.M. *Amer. J. Physiol.* **246**, E1-E13, 1984). In recent years, studies in transgenic animals have confirmed that GK does indeed
20 play a critical role in whole-body glucose homeostasis. Animals that do not express GK die within days of birth with severe diabetes while animals overexpressing GK have improved glucose tolerance (Grupe, A., Hultgren, B., Ryan, A. et al., *Cell* **83**, 69-78, 1995; Ferrie, T., Riu, E., Bosch, F. et al., *FASEB J.*, **10**, 1213-1218, 1996). An increase in glucose exposure is coupled through GK in β -cells to increased insulin secretion and in
25 hepatocytes to increased glycogen deposition and perhaps decreased glucose production.

The finding that type II maturity-onset diabetes of the young (MODY-2) is caused by loss of function mutations in the GK gene suggests that GK also functions as a glucose sensor in humans (Liang, Y., Kesavan, P., Wang, L. et al., *Biochem. J.* **309**, 167-173, 1995). Additional evidence supporting an important role for GK in the regulation of glucose metabolism in humans was provided by the identification of patients that express a mutant form of GK with increased enzymatic activity. These patients exhibit a fasting hypoglycemia associated with an inappropriately elevated level of plasma insulin (Glaser, B., Kesavan, P., Heyman, M. et al., *New England J. Med.* **338**, 226-230, 1998). While mutations of the GK gene are not found in the majority of patients with type II diabetes, compounds that activate GK and, thereby, increase the sensitivity of the GK sensor system will still be useful in the treatment of the hyperglycemia characteristic of all type II diabetes. Glucokinase activators will increase the flux of glucose metabolism in β -cells and hepatocytes, which will be coupled to increased insulin secretion. Such agents would be useful for treating type II diabetes.

This invention provides a compound, comprising an amide of the formula:



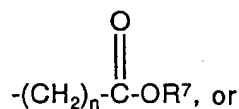
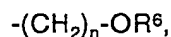
wherein X is -O- or



R is a heteroaromatic ring, connected by a ring carbon atom, which contains from 5 to 6 ring members with from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur or nitrogen; aryl containing 6 or 10 ring carbon atoms, aryl fused with a heteroaromatic ring which contains from 5 to 6 ring members with 1 to 3 heteroatoms in the ring being selected from the group consisting of nitrogen, oxygen or sulfur, a saturated 5- or 6-membered cycloheteroalkyl ring which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, or a cycloalkyl ring having 5 or 6 carbon atoms; R¹ is a cycloalkyl ring having from 5 or 6 carbon atoms; R² is

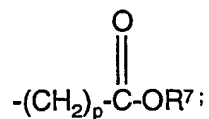


a five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amide group shown, which contains from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen with a first heteroatom being nitrogen adjacent to the connecting ring carbon atom, said heteroaromatic ring being unsubstituted or monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl,



20

n is 0, 1, 2, 3 or 4; y and z are independently 0 or 1; R³ is hydrogen, lower alkyl or



R^6 , R^7 and R^8 are independently hydrogen or lower alkyl; p is an integer from 0 to 5; and $*$ denotes the asymmetric carbon atom center; or a pharmaceutically acceptable salt thereof.

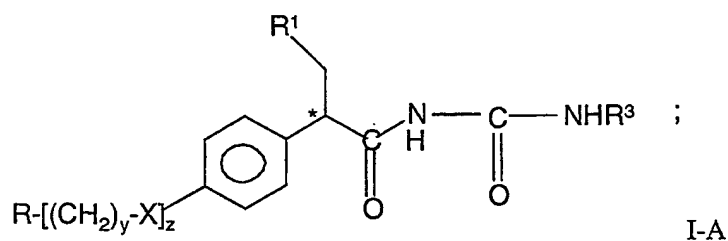
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The compounds of formula I are glucokinase activators are useful for increasing insulin secretion in the treatment of type II diabetes.

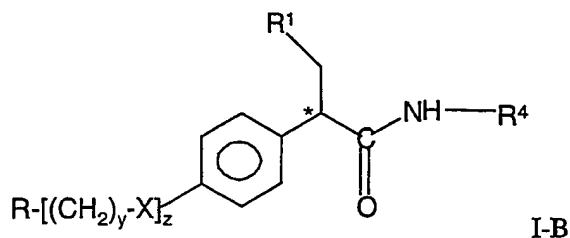
The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier and/or adjuvant. Furthermore, the present invention relates to the use of such compounds as therapeutic active substances as well as to their use for the preparation of medicaments for the treatment or prophylaxis of type II diabetes. The present invention further relates to processes for the preparation of the compounds of formula I. In addition, the present invention relates to a method for the prophylactic or therapeutic treatment of type II diabetes, which method comprises administering a compound of formula I to a human being or an animal.

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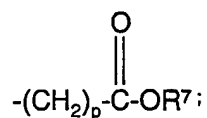
The compounds of formula I have the following embodiments



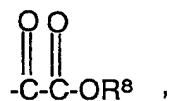
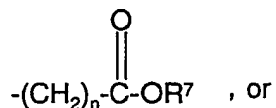
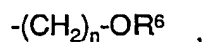
and



wherein *, R, R¹, X, y, n and z are as above; and R³ is hydrogen, lower alkyl or



- 5 wherein R⁷ and p are as above; preferably, R³ is hydrogen or lower alkyl;
 R⁴ is a five- or six-membered heteroaromatic ring connected by a ring carbon atom to the
 amide group shown, which heteroaromatic ring contains from 1 to 3 heteroatoms selected
 from the group consisting of oxygen, sulfur and nitrogen with a first heteroatom being
 nitrogen adjacent to the connecting ring carbon atom, said heteroaromatic ring, preferably
 10 thiazolyl or pyridyl, being unsubstituted or monosubstituted at a position on a ring carbon
 atom other than adjacent to said connecting carbon atom with a substituent selected from
 the group consisting of lower alkyl,



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n is 0, 1, 2, 3 or 4;

R⁶, R⁷ and R⁸ are independently hydrogen or lower alkyl;

or a pharmaceutically acceptable salt thereof.

In the compound of formulae I, IA and IB, the "*" designates the asymmetric carbon atom in this compound with the R optical configuration being preferred. The compounds of formula I may be present in the pure R form or as a racemic or other mixtures of compounds having the R and S optical configuration at the asymmetric carbon shown. The pure R enantiomers are preferred.

As used throughout this application, the term "lower alkyl" includes both straight chain and branched chain alkyl groups having from 1 to 7 carbon atoms, such as methyl, ethyl, propyl, isopropyl, preferably methyl and ethyl. As used herein, the term "halogen or halo" unless otherwise stated, designates all four halogens, i.e. fluorine, chlorine, bromine and iodine.

R can be any five- or six-membered saturated cyclic heteroalkyl ring containing from 1 to 2 heteroatoms selected from the group consisting of sulfur, oxygen or nitrogen. Any such five- or six-membered saturated heterocyclic ring can be used in accordance with this invention. Among the preferred rings are morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, etc.

As used herein, the term "aryl" signifies "polynuclear" and mononuclear unsubstituted aromatic hydrocarbon groups such as phenyl or naphthyl containing either 6 or 10 carbon atoms.

The heteroaromatic ring defined by R, R² and R⁴ can be five- or six-membered heteroaromatic ring having from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur which is connected by a ring carbon to the remainder of the molecule as shown. The heteroaromatic ring defined by R² and R⁴ contains a first nitrogen heteroatom adjacent to the connecting ring carbon atom and if present, the other heteroatoms can be oxygen, sulfur, or nitrogen. Among the preferred heteroaromatic rings include pyridinyl, pyrimidinyl and thiazolyl. On the other hand, the heteroaromatic ring defined by R need not contain a nitrogen heteroatom. These heteroaromatic rings which constitute R² or R⁴ are connected *via* a ring carbon atom to the amide group to form the

amides of formula I. The ring carbon atom of the heteroaromatic ring which is connected via the amide linkage to form the compound of formula I does not contain any substituent. When R^2 or R^4 is an unsubstituted or mono-substituted five- or six-membered heteroaromatic ring, the rings contain a nitrogen heteroatom adjacent to the connecting
5 ring carbon.

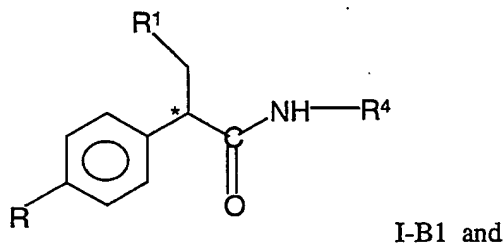
When R is aryl fused with a heteroaromatic ring, the term "aryl" is as defined above and the term "heteroaromatic" is as defined above. In the compounds of formulae I, IA and IB, the preferred aryl is phenyl. The heteroaromatic substituent is connected to the
10 remainder of the molecule through the aryl substituent. The preferred heteroaromatic ring formed by fusing to aryl substituents which define R, are indolyl, quinolyl, isoquinolyl, 2H-chromanlyl and benzo[b]thienyl. When R is a cycloalkyl group, R can be any cycloalkyl group containing 5 or 6 carbon atoms such as cyclohexyl or cyclopentyl.

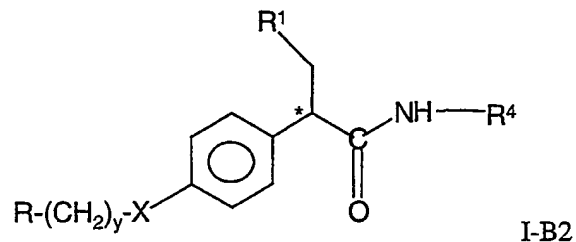
15 The term "amino protecting group" designates any conventional amino protecting group which can be cleaved to yield the free amino group. The preferred protecting groups are the conventional amino protecting groups utilized in peptide synthesis. Especially preferred are those amino protecting groups which are cleavable under mildly acidic conditions from about pH 2.0 to 3. Particularly preferred amino protecting groups
20 such as t-butoxycarbonyl carbamate, benzyloxycarbonyl carbamate, 9-fluorenylmethyl carbamate.

The term "pharmaceutically acceptable salts" as used herein include any salt with both inorganic or organic pharmaceutically acceptable acids such as hydrochloric acid,
25 hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulfonic acid, *para*-toluene sulfonic acid and the like. The term "pharmaceutically acceptable salts" also includes any pharmaceutically acceptable base salt such as amine salts, trialkyl amine salts and the like. Such salts can be formed quite readily by those skilled in the art using standard
30 techniques.

During the course of the reaction the various functional groups such as the free carboxylic acid or hydroxy groups will be protected *via* conventional hydrolyzable ester or ether protecting groups. As used herein the term "hydrolyzable ester or ether protecting groups" designates any ester or ether conventionally used for protecting carboxylic acids or alcohols which can be hydrolyzed to yield the respective hydroxyl or carboxyl group. Exemplary ester groups useful for those purposes are those in which the acyl moieties are derived from a lower alkanolic, aryl lower alkanolic, or lower alkane dicarboxylic acid. Among the activated acids which can be utilized to form such groups are acid anhydrides, acid halides, preferably acid chlorides or acid bromides derived from aryl or lower alkanolic acids. Example of anhydrides are anhydrides derived from monocarboxylic acid such as acetic anhydride, benzoic acid anhydride, and lower alkane dicarboxylic acid anhydrides, e.g. succinic anhydride as well as chloro formates e.g. trichloro, ethylchloro formate being preferred. A suitable ether protecting group for alcohols are, for example, the tetrahydropyranyl ethers such as 4-methoxy-5,6-dihydroxy-2H-pyranyl ethers. Others are aroylmethylethers such as benzyl, benzhydryl or trityl ethers or α -lower alkoxy lower alkyl ethers, for example, methoxymethyl or allylic ethers or alkyl silylethers such as trimethylsilylether.

The compounds of formula I-B have the following embodiments:

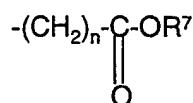




wherein X, R, R¹, R⁴, * and y are as above.

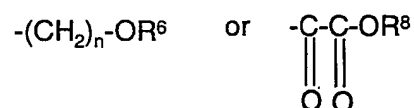
Among the compounds of formulae IB-1 and IB-2 are those compounds where R¹ is cyclopentyl, i.e., the compounds of formulae I-B1(a) and I-B2(a). Among the embodiments of compounds of formula I-B1(a) are those compounds where R is aryl [the compound of formula I-B1(a)(1)]. Among those compounds of formula I-B1(a)(1) are those compounds where R⁴ is

- (a) an unsubstituted thiazolyl;
 (b) thiazolyl substituted with



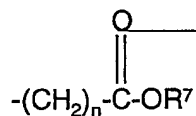
wherein n and R⁷ are as above;

- (c) thiazolyl substituted with



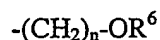
where n, R, R⁶ and R⁸ are as above;

- (d) an unsubstituted pyridinyl;
 (e) pyridinyl monosubstituted with



where n and R⁷ are as above; or

- (f) pyridinyl monosubstituted with



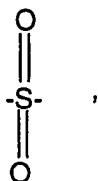
where R^6 and n are as above.

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Among the embodiments of compounds of formula I-B1(a) are those compounds where R is a heteroaromatic ring containing from 5 to 6 ring members with from 1 to 2 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur. In this case, the preferred embodiments are those compounds where R^4 is an unsubstituted
 10 pyridinyl or thiazolyl. In accordance with this preferred embodiment, where R^4 is pyridinyl or thiazolyl, the heteroaromatic substituent defined by R is, most preferably, also pyridinyl or thiophenyl.

Other embodiments of the compounds of formula I-B1(a) are those compounds
 15 where R is aryl fused to a 5- or 6-membered heteroaromatic ring containing from 1 to 2 heteroatoms in the ring selected from the group consisting of oxygen, sulfur and nitrogen. In this case, the preferred embodiment are those compounds where R^4 is thiazolyl. Among the embodiments of compounds of formula I-B2(a) are those compounds where X is -O- [the compound of formula I-B2(a)(1)]. Among the embodiments of the formula of
 20 I-B2(a)(1) are compounds where R is aryl. In this case, the preferred compounds are those where R^4 is unsubstituted or substituted pyridinyl or thiazolyl.

Among the embodiments of the compounds of formula I-B2(a) are those
 25 compounds where X is

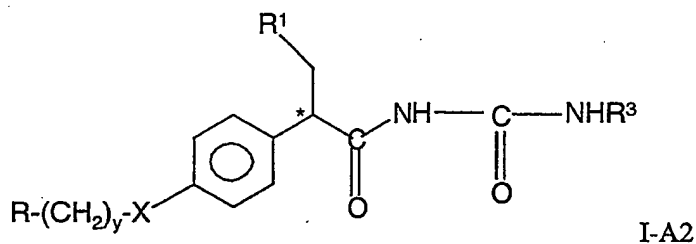
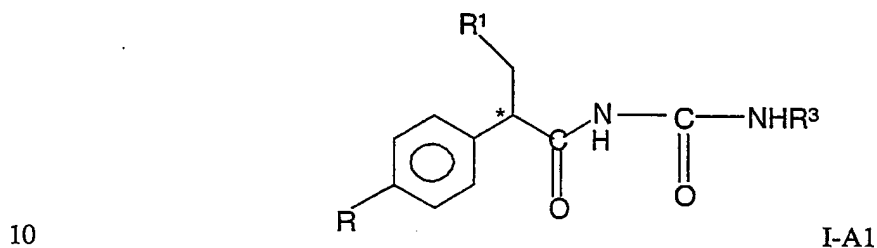


the compounds of formula I-B2(a)(2). Among the embodiments of the compounds of formula I-B2(a)(2) are those compounds where R is aryl, with compounds where R^4 is

thiazolyl being especially preferred. Among the embodiments of the compounds of formula I-B(2)a(2) are those compounds where R is cycloalkyl and R⁴ is thiazolyl.

Among the embodiments of the compounds of formula I-B2(a)(2) are those compounds where R is a heteroaromatic ring and preferably, in this case those compounds where R⁴ is thiazolyl.

The compounds of formula I-A have the following embodiments:



15 where X, R, R¹, R³ and y are as above.

Among the embodiments of compounds of the formulae I-A1 and I-A2 are those compounds where R¹ is cyclopentyl, i.e., the compounds of formulae I-A1(a) and I-A2(a). Among the embodiments of the compounds of formulae I-A1(a) and I-A2(a) are those compounds where

(a) R is aryl;

- (b) R is a 5- or 6-membered heteroaromatic ring containing from 1 to 3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur;
- (c) R is a saturated 5- or 6-membered cycloheteroalkyl ring containing from 1 to 2 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; and
- (d) R is cycloalkyl.

In one embodiment of the present invention, R¹ is cyclopentyl. In another embodiment, R is phenyl or naphthyl. In still another embodiment, R is a heteroaromatic ring, connected by a ring carbon atom, which contains from 5 to 6 ring members with from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur or nitrogen, with thienyl, pyridyl and imidazolyl being preferred. In still another embodiment, R is phenyl or naphthyl fused with a heteroaromatic ring containing 5 or 6 ring members with 1 or 2 heteroatoms in the ring being selected from the group consisting of nitrogen, oxygen or sulfur, with indolyl being preferred. In still another embodiment, R is a saturated 5- or 6-membered cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen, with morpholinobeing preferred. In still another embodiment, R is cyclopentyl or cyclohexyl.

In one embodiment of the present invention, X is -SO₂-. In another embodiment of the present invention, X is -O-. In another embodiment of the present invention, z is 0. In another embodiment of the present invention, z is 1. In one embodiment of the present invention, y is 0. In another embodiment of the present invention, y is 1.

In a preferable embodiment of the present invention, n is 0, 1 or 2. Preferable residue R⁶ is hydrogen, preferable residue R⁸ is lower alkyl.

Preferable compounds in accordance with the present invention are compounds of above formula I, wherein X is -O- or -S(O)₂-; R is a heteroaromatic ring, connected by a ring carbon atom, which contains from 5 to 6 ring members with from 1 to 2 heteroatoms

selected from sulfur or nitrogen, aryl containing 6 or 10 ring carbon atoms, aryl containing from 6 to 10 ring carbon atoms fused with a heteroaromatic ring containing 5 ring members with 1 nitrogen atom in the ring; or a saturated 6-membered cycloheteroalkyl ring, which contains 2 heteroatoms selected from oxygen and nitrogen; or a cycloalkyl ring having 5 or 6 carbon atoms; R¹ is a cycloalkyl ring having 5 carbon atoms; R² is –C(O)-NHR³, a five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amide group shown, which heteroaromatic ring contains 1 or 2 heteroatoms selected from sulfur and nitrogen with a first heteroatom being nitrogen which is adjacent to the connecting ring carbon atom, said heteroaromatic ring being unsubstituted or monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, -(CH₂)_n-OR⁶, -(CH₂)_n-C(O)OR⁷, or -C(O)-C(O)OR⁸; n is 0, 1 or 2; y and z are independently 0 or 1, * denotes the asymmetric carbon atom center; R³ is hydrogen or lower alkyl; R⁶ is hydrogen; R⁷ is hydrogen or lower alkyl; and R⁸ is lower alkyl.

15

Most preferable compounds in accordance with the present invention are:

2-biphenyl-4-yl-3-cyclopentyl-N-thiazol-2-yl-propionamide,

(2R)-2-biphenyl-4-yl-3-cyclopentyl-N-thiazol-2-yl-propionamide,

3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-N-thiazol-2-yl-propionamide,

20 [2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazol-4-yl]-acetic acid methyl ester,

[2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazol-4-yl]-acetic acid ethyl ester,

25 2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazole-4-carboxylic acid ethyl ester,

2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazole-4-carboxylic acid methyl ester,

{2-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid methyl ester,

30 {2-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester,

2-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester,

[2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazol-4-yl]-oxo-acetic acid ethyl ester,

5 2-biphenyl-4-yl-3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-propionamide,
2-biphenyl-4-yl-3-cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-propionamide,
3-cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-2-(4-naphthalen-1-yl-phenyl)-propionamide,

3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-naphthalen-1-yl-phenyl)-propionamide,

10 2-biphenyl-4-yl-3-cyclopentyl-N-pyridin-2-yl-propionamide,
3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-N-pyridin-2-yl-propionamide,
6-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-nicotinic acid methyl ester,
6-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-nicotinic acid,

15 2-biphenyl-4-yl-3-cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-propionamide,
6-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-nicotinic acid methyl ester,

6-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-nicotinic acid,
3-cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-2-(4-naphthalen-1-yl-phenyl)-propionamide,

20 3-cyclopentyl-N-thiazol-2-yl-2-(4-thiophen-2-yl-phenyl)-propionamide,
3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-N-thiazol-2-yl-propionamide,
3-cyclopentyl-N-pyridin-2-yl-2-(4-pyridin-4-yl-phenyl)-propionamide,
25 3-cyclopentyl-N-pyridin-2-yl-2-(4-pyridin-3-yl-phenyl)-propionamide,
3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-N-thiazol-2-yl-propionamide,
2-(4-benzyloxy-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
3-cyclopentyl-2-(4-phenoxy-phenyl)-N-thiazol-2-yl-propionamide,
30 3-cyclopentyl-2-(4-phenoxy-phenyl)-N-pyridin-2-yl-propionamide,

{2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester,

3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-phenoxy-phenyl)-propionamide,

5 2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester,

3-cyclopentyl-N-[4-(2-hydroxy-ethyl)-thiazol-2-yl]-2-(4-phenoxy-phenyl)-propionamide,

10 {2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid,

{2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid methyl ester,

3-cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-phenoxy-phenyl)-propionamide,

15 6-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-nicotinic acid methylester,

6-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-nicotinic acid,

3-cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-2-(4-phenoxy-phenyl)-propionamide,

2-(4-benzenesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,

20 2-(4-cyclopentanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,

2-(4-cyclohexanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,

3-cyclopentyl-2-[4-(1H-imidazole-2-sulfonyl)-phenyl]-N-thiazol-2-yl-propionamide,

(2-biphenyl-4-yl-3-cyclopentyl-propionyl)-urea,

25 1-(2-biphenyl-4-yl-3-cyclopentyl-propionyl)-3-methyl-urea,

1-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionyl]-3-methyl-urea,

1-[3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionyl]-3-methyl-urea,

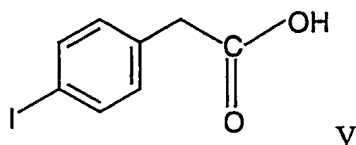
1-{3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-propionyl}-3-methyl-urea,

1-[3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-propionyl]-3-methyl-urea,

30 1-[2-(4-cyclohexanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea, and

1-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionyl]-3-methyl-urea.

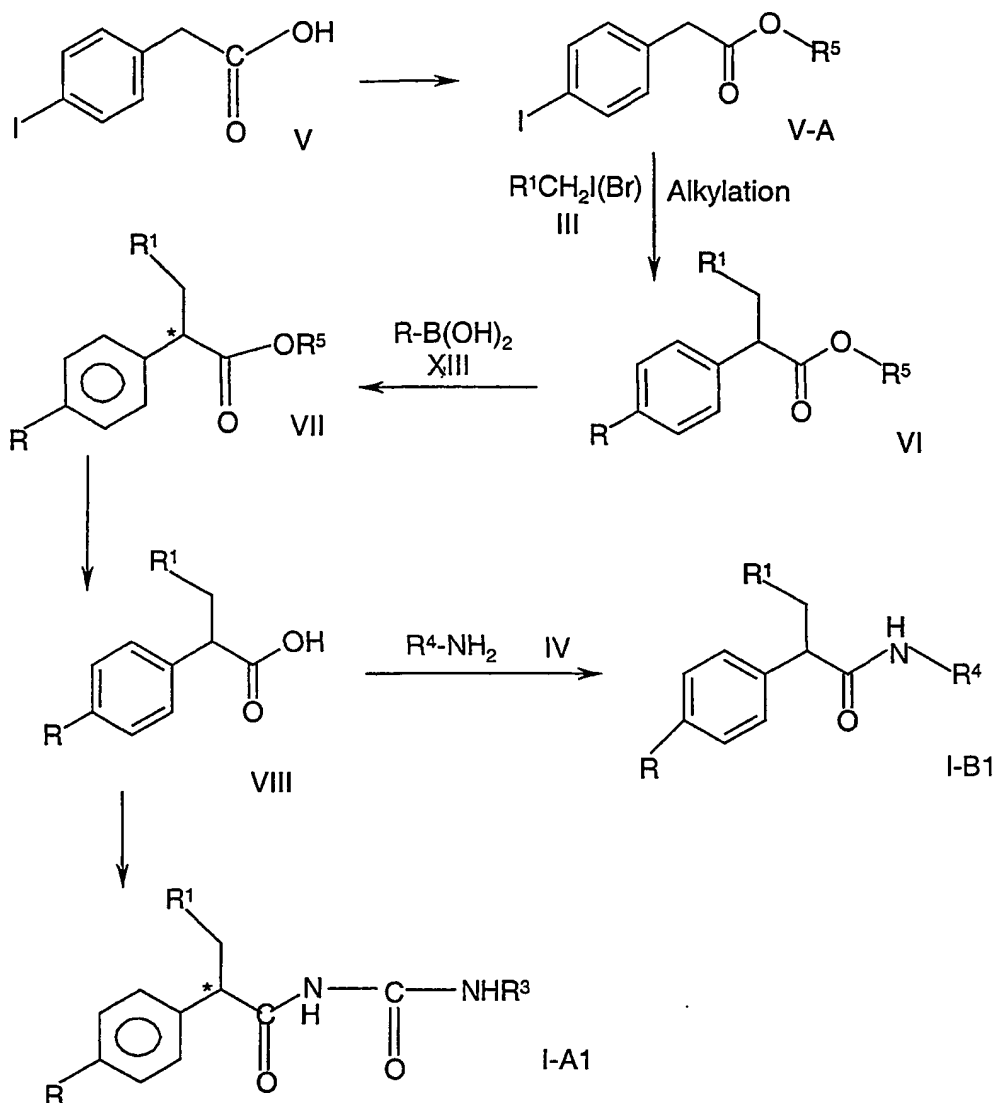
The compounds of formulae I-B1 and I-A1 can be prepared from compounds of the formula



5

The compounds of formulae IB-1 and IA-1 are produced from the compound of formula V via the following reaction scheme:

10



wherein R, R¹, R³ and R⁴ are as above and R⁵, taken together with its attached oxygen atom forms a hydrolyzable ester.

In the first step of this reaction, the carboxylic acid group of the compound of formula V is protected by converting it to a hydrolyzable ester protecting group. In this conversion, the compound of formula V is converted to the compound of formula V-A

treating the compound of formula V with an organic alcohol such as a lower alkanol in the presence of a strong inorganic acid such as sulfuric acid. In carrying out this reaction, any conventional method of esterification can be utilized. In accordance with the preferred embodiment, the ester of formula V-A is a methyl ester produced by reacting the compound of formula V with methanol utilizing sulfuric acid as an esterification catalyst.

5 In the next step, the compound of formula V-A is alkylated with the compound of formula III to produce the compound of formula VI. Any conventional method of alkylating the alpha carbon atom of an organic acid ester with an alkyl bromide or iodide can be utilized to effect this conversion and produce the compound of formula VI. In the next step of this

10 reaction, the compound of formula VI is coupled with the compound of formula XIII to produce the compound of formula VII via a Suzuki coupling reaction. These coupling reactions are carried out in an inert organic polar solvent, preferably dimethylformamide and dimethoxyethane utilizing a tertiary amine such as tri-lower alkyl amine, preferably tri-ethylamine and a ligand forming reagent. Among the preferred ligand forming

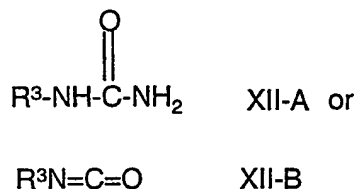
15 reagents are tri-lower alkyl or tri-aryl phosphines. This reaction is carried out in the presence of a noble metal catalyst such as a palladium II catalysts, preferably palladium diacetate. In carrying out this reaction, temperatures of from 80°C. to the reflux temperature of a solvent medium are utilized. In the next step, the compound of formula VII is converted to the compound of formula VIII by hydrolyzing the R⁵ protecting group

20 to form the corresponding organic acid of formula VIII. Any conventional method of hydrolyzing an ester can be utilized to effect this conversion. In the next step of this process, the organic acid of formula VIII is reacted with the amine of formula IV to produce the compound of formula I-B1. This reaction is carried out by condensing the compound of formula IV with the compound of formula VIII to form the amide of

25 formula I-B1. This condensation reaction can be carried out utilizing any of the conventional means for amide formation.

On the other hand, the compound of formula VIII can be converted to the compound of formula IA-1. The coupling of the compound of formula VIII with either

30 compounds of the formulae



wherein R^3 is as above

produces the compound of formula IA-1.

5

The carboxylic acid of formula VIII can be converted to the corresponding amide. This amide formation is carried out in two steps first by converting the carboxylic acid of formula VIII to the corresponding acid chloride and then by reacting this acid chloride with ammonia. Any of the conditions conventional for converting a carboxylic acid to a corresponding carboxylic acid chloride can be utilized in this procedure. Furthermore the reactions of carboxylic acid chloride with ammonia to produce the corresponding amide is also a well known reaction and the conditions conventional in this well known reaction can be utilized in the formation of the amide corresponding to the compound of formula VIII. The amide is then reacted with the isocyanate of formula XII-B to form the urea adduct of the compound of formula I-A1. Any conventional method of reacting an isocyanate with an amide to form a urea linkage can be utilized to produce the compound of formula I-A1. On the other hand, the acid chloride can directly reacted with the compound of urea reagent formula XII-A to produce a urea adduct. Any of the conditions conventional in a method of reacting a chloride with a urea reagent can be utilized in carrying out this procedure.

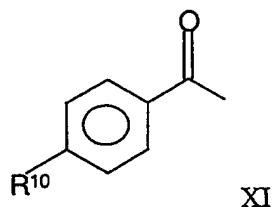
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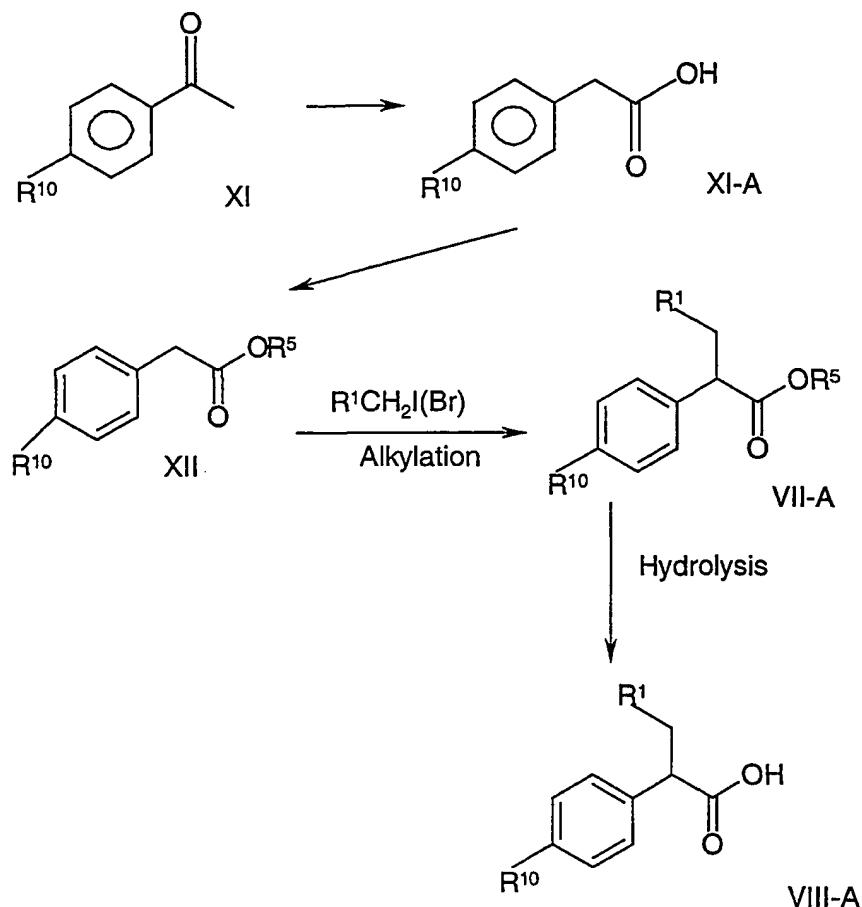
The compound of formula V-A wherein R is cycloalkyl or aryl are known compounds. On the other hand, compounds of formula V-A wherein R is a heteroaromatic ring or a saturated 5 to 6-membered heteroalkyl ring or aryl fused with a heteroaromatic ring can be prepared from known compounds of formula:

25



wherein R^{10} is a heteroaromatic ring containing from 5 to 6 ring members with from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen; a saturated 5- or 6-membered cycloheteroalkyl ring containing from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen; or aryl fused with a heteroaromatic ring which contain 5 or 6 ring members with 1 to 3 heteroatoms in the ring being selected from the group consisting of nitrogen, oxygen and sulfur.

The compound of formula XI is converted to the compound of formula VIII, where R is R^{10} (the compound of formula VIII-A), by the following reaction scheme:



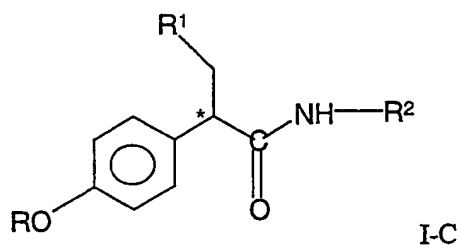
wherein R¹, R⁵ and R¹⁰ are as above.

5

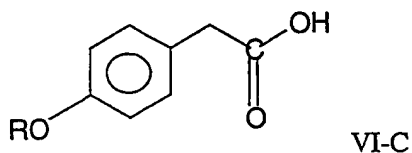
The compound of formula XI is converted to the compound of formula XI-A by utilizing any conventional means of converting an acetophenone to acetic acid. In general, this reaction is carried out by treating the compound of formula XI with morpholine in a inert organic solvent while heating to a temperature of above 80°C. to reflux. While this is
 10 done, acetic acid and sulfuric acid are added to the reaction mixture to cause the methyl ketone to convert to acetic acid derivative of formula XI-A. The compound of formula XI-A is esterified with a conventional esterifying agent so that the free acid forms a hydrolyzable ester of formula XII. This reaction is carried out utilizing the same

procedure described in connection with the conversion of the compound of formula V to the compound of formula V-A. The compound of formula XII is then alkylated with the compound of formula III to produce the compound of formula VII-A. This reaction is carried out in the same manner as disclosed in connection with the conversion of the compound of formula V-A to the compound of formula VI. The compound of formula VII-A is then hydrolyzed as described hereinbefore in connection with the conversion of the compound of formula VII to the compound formula VIII to produce to the compound of formula VIII-A. The compound of formula VIII-A can be converted to the compounds of formulae I-A1 and I-B1, where R is R¹⁰, in the manner described herein before in connection with the conversion of the compound of formula VIII to the compounds of formulae I-A1 and I-B1.

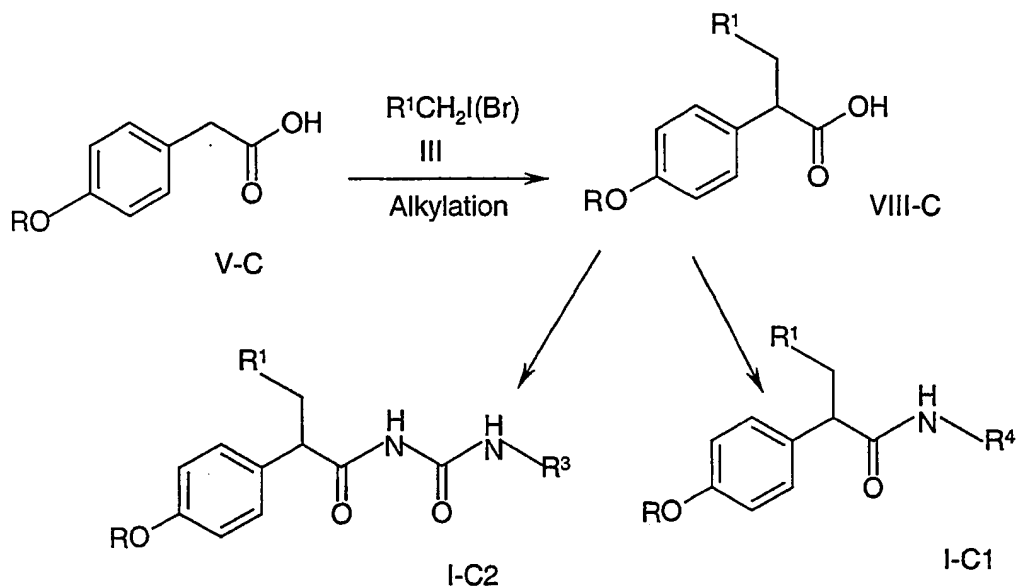
When in the compound of formula I, when X is -O-, y is 0 and z is 1, i.e., compounds of the formula



wherein R, R¹ and R² are as above,
these compounds are prepared from compounds of the formula



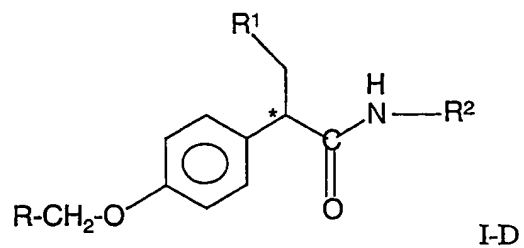
via the following reaction scheme:



wherein R, R¹, R³ and R⁴ are as above.

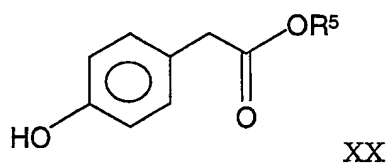
5 The compound of the formula V-C is converted to the compound of formula VIII-C by alkylation with the compound of formula III in the same manner described in connection with the conversion of the compound of formula V-A to the compound of formula VI. The compound of formula VIII-C can be converted to the compound of formula I-C1 in the same manner as described for the conversion of the compound of
 10 formula VIII to the compound of formula I-B1. On the other hand, the compound of formula VIII-C can be converted to the compound of formula I-C2 in the same manner as described in connection with the conversion of compound of formula VIII into the compound of formula I-A1.

15 On the other hand, when X is O and y is 1, the compound of formula:



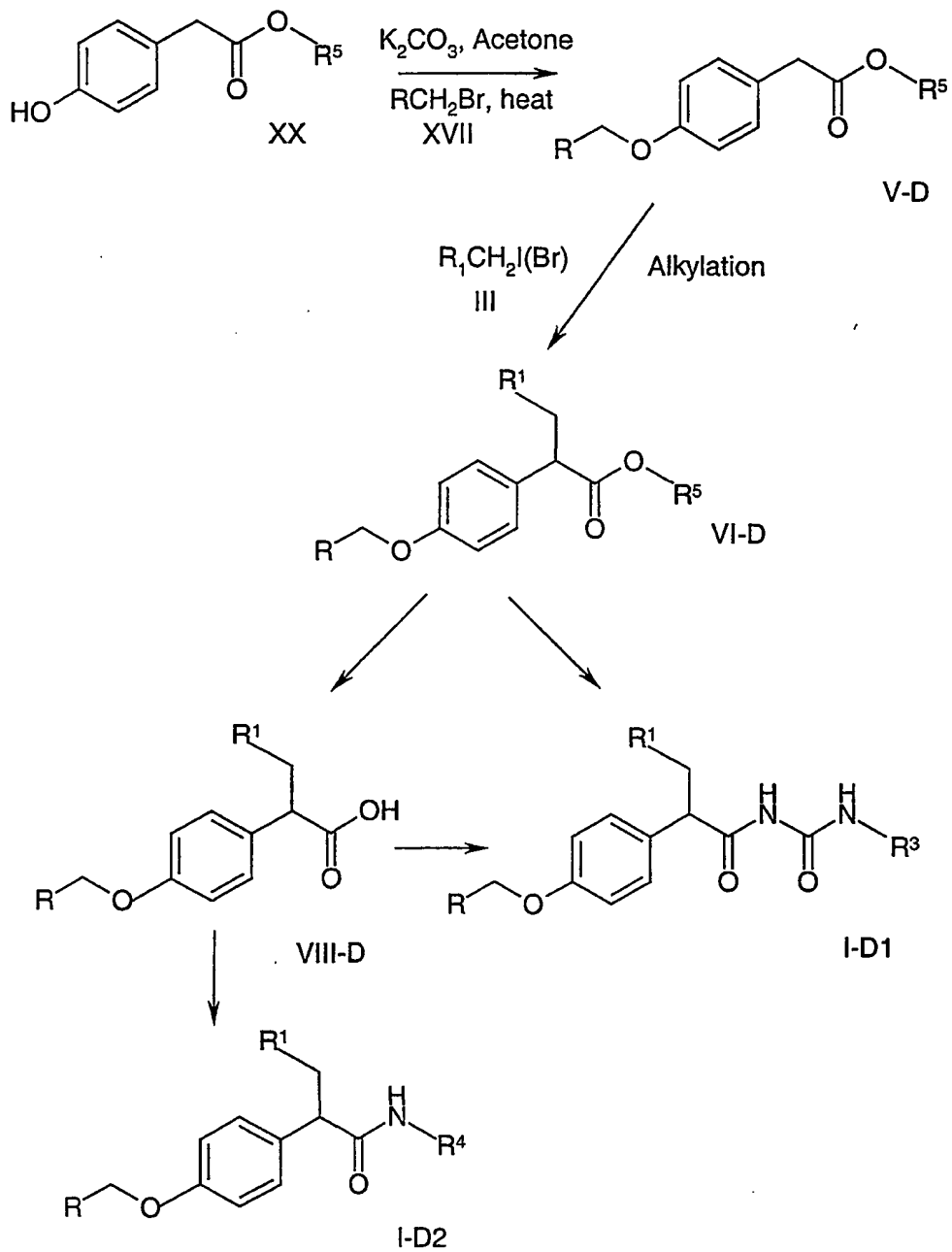
wherein R, R¹ and R² are as above.

5 These compounds can be prepared from compounds of the formula



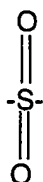
10 wherein R⁵ is as above,

via the following reaction scheme:

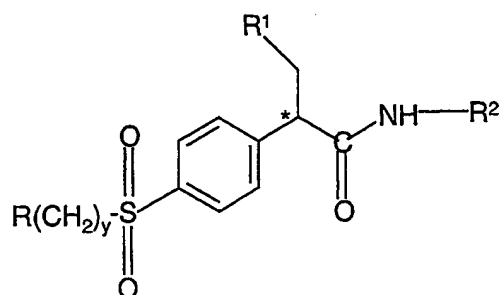


The compound of formula XX is condensed with the compound of formula XVII to produce the compound of formula V-D utilizing any of the known procedures for condensing an alcohol with an alkyl bromide to form an ether. Any of the conditions conventionally utilized in forming an ether by utilizing a bromide and an alcohol can be
5 utilized to affect this conversion. In accordance with the preferred embodiment of this invention, this reaction is carried out in the presence of an alkaline earth metal carbonate in the presence of an organic solvent such as acetone. In carrying out this reaction, elevated temperatures are utilized, i.e., temperatures of from about 80°C. to reflux. The compound of formula V-D is converted to the compound of formula VI-D utilizing the
10 same procedure described in connection with the reaction of the compound of formula III with the compound of formula V-A to produce the compound of formula VI. The compound of formula VI-D is converted to the compound of formula VIII-D by conventional hydrolysis as described hereinbefore. The compound of formula VIII-D can be converted to the compound of formula I-D2 in the same manner as described herein in
15 connection with the conversion of formula VIII to the compound of formula I-B1. On the other hand, the compound of formula VIII-D can be converted to the compound of formula I-D1 utilizing the same procedure as described hereinbefore in converting the compound of formula VIII to the compound of formula I-A1.

20 In accordance with another embodiment of this invention, the compound of formula I wherein y is 0 or 1 and X is

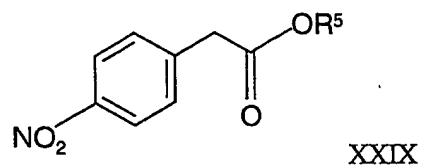


25 i.e., a compound of the formula



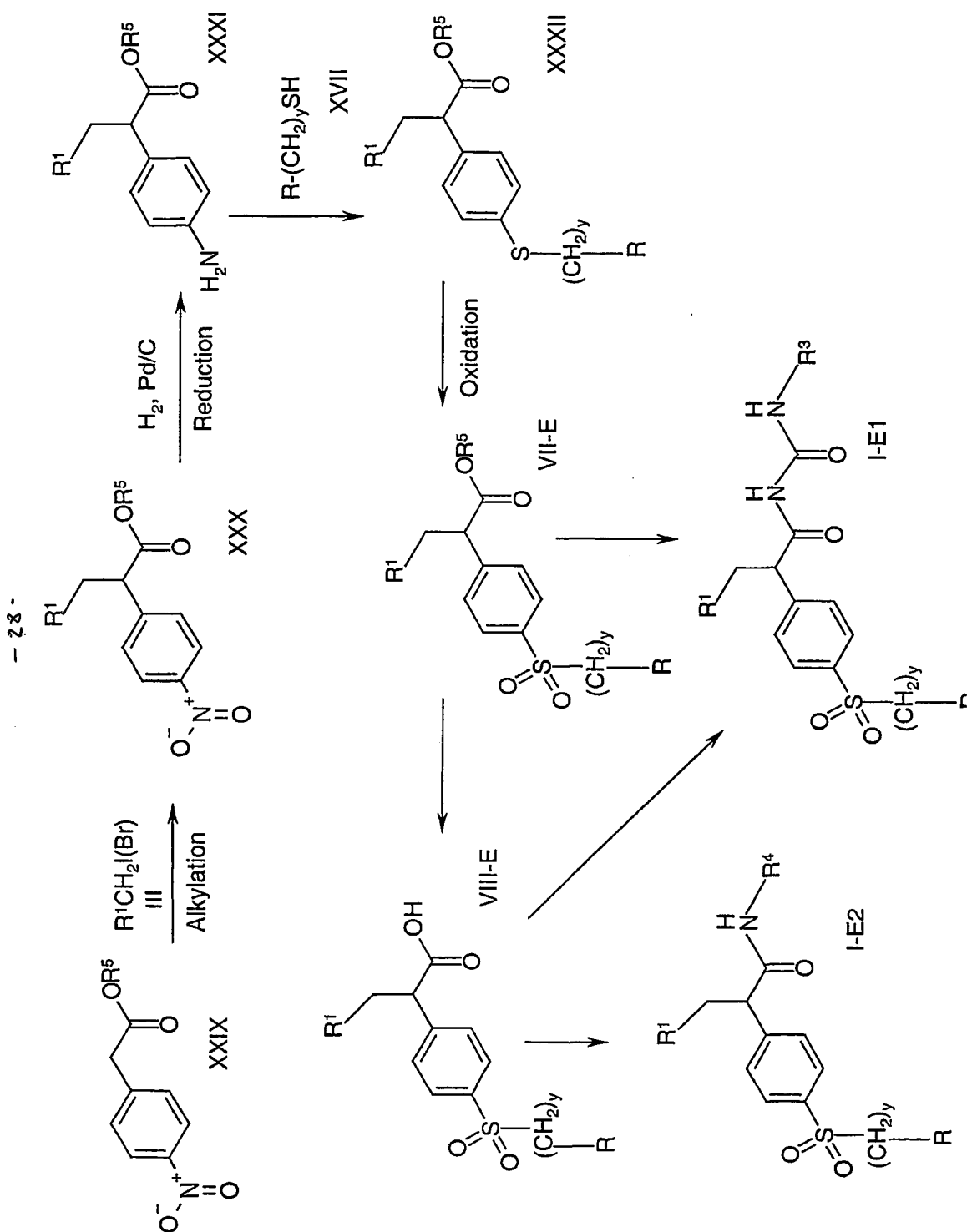
wherein y , R , R^1 and R^2 are as above,
 can be prepared from a compound of the formula

5



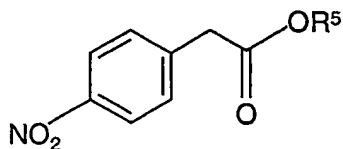
wherein R^5 is as above,
 via the following reaction scheme:

10

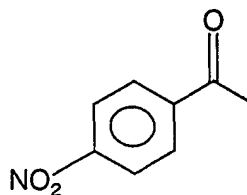


In this procedure, the compound of formula XXIX is reacted with the compound of formula III via an alkylation reaction to produce the compound of formula XXX. This alkylation reaction is carried out in the same manner described in connection with the alkylation compound of formula V-A to the compound of formula VI by the reaction of the compound of formula VI-A with the compound of formula III. The compound of formula XXX is converted to the compound of formula XXXI by conventional reduction of a nitro group to an amine group. Any of the conditions conventional in reducing a nitro group to an amine group can be utilized. Among the preferred methods are hydrogenation over palladium carbon catalyst. The step of converting the compound of formula XXX to the compound of formula XXXI is carried out through the use of such conventional reduction techniques. In the next step of this reaction of compound of formula XXXI is converted the compound of formula XXXII by reacting the compound of formula XXXI with the compound of formula XVII. This is carried out by conventional means such as converting a phenylamino group to a phenylthio group by elimination of the amino substituent and the addition of the thio substituent to the phenyl ring. In the next step of the process, the compound of formula XXXII is converted to the compound of formula VII-E by oxidizing the thio group to a sulfone group. Any conventional method of oxidizing a thio to a sulfone group can be utilized in carrying out this procedure. The compound of formula VII-E is converted to the compound of formula VIII-E by conventional ester hydrolysis. The compound of formula VIII-E is converted to the compound of formula I-E1 in accordance with the procedure already described in connection with the conversion of a compound of formula VIII to a compound of formula I-A1. On the other hand, the compound of formula VIII-E can be converted to the compound of formula I-E2 by the same procedure hereinbefore described in connection with the conversion of the compound of formula VIII to a compound of formula I-B1.

Those phenyl compounds of the formula



or



5 are known compounds. When one wants to prepare the corresponding para iodo substituted phenyl compounds, these para iodo substituted phenyl compounds are formed from these known para nitro phenyl compounds listed above. The para nitro group can then be reduced to an amino group. Any conventional method of reducing a nitro group to an amine can be utilized to effect this conversion. This amine group can be used to
 10 prepare the corresponding para iodo compound via a diazotization reaction. Any conventional method of converting amino group to an iodo group (see, for example, Lucas, H. J.; Kennedy, E. R. *Org. Synth. Coll. Vol., II* **1943**, 351) can be utilized to effect this conversion.

15 The compound of formula I, "*" designates an asymmetric carbon atom through which the group $-\text{CH}_2\text{R}^2$ and the acid amide substituents are connected. In accordance with this invention, the preferred stereoconfiguration of this group is R.

If it is desired to produce the "R" or the S isomer of the compound of formula I, this
 20 compound can be separated into these isomers by any conventional chemical means. Among the preferred chemical means is to react the free acid compounds of formulae VIII, VIII-A, VIII-C, VIII-D or VIII-E with an optically active base. Any conventional optically active base can be utilized to carry out this resolution. Among the preferred optically active bases are the optically active amine bases such as alpha-methylbenzylamine, quinine, dehydroabietylamine and alpha-methylnaphthylamine. Any
 25 methylbenzylamine, quinine, dehydroabietylamine and alpha-methylnaphthylamine. Any

of the conventional techniques utilized in resolving organic acids with optically active organic amine bases can be utilized in carrying out this reaction.

In the resolution step, the compound of formula VIII is reacted with the optically
5 active base in an inert organic solvent medium to produce salts of the optically active
amine with both the R and S isomers of this compound of formula VIII. In the formation
of these salts, temperatures and pressure are not critical and the salt formation can take
place at room temperature and atmospheric pressure. The R and S salts can be separated
by any conventional method such as fractional crystallization. After crystallization, each
10 of the salts can be converted to the respective compounds of formula VIII in the R and S
configuration by hydrolysis with an acid. Among the preferred acids are dilute aqueous
acids, i.e., from about 0.001N to 2N aqueous acids, such as aqueous sulfuric or aqueous
hydrochloric acid. The configuration of formula VIII which are produced by this method
of resolution is carried out throughout the entire reaction scheme to produce the desired R
15 or S isomer of formula I. The separation of R and S isomers can also be achieved using
an enzymatic ester hydrolysis of any lower alkyl esters corresponding to the compound of
the formula VIII (see for example, Ahmar, M.; Girard, C.; Bloch, R, *Tetrahedron Lett*,
1989, 7053), which results in the formation of corresponding chiral acid and chiral ester.
The ester and the acid can be separated by any conventional method of separating an acid
20 from an ester. The preferred method of resolution of racemates of the compounds of the
formula VIII is via the formation of corresponding diastereomeric esters or amides.
These diastereomeric esters or amides can be prepared by coupling the carboxylic acids
of the formula VIII with a chiral alcohol, or a chiral amine. This reaction can be carried
out using any conventional method of coupling a carboxylic acid with an alcohol or an
25 amine. The corresponding diastereomers of compounds of the formula VIII can then be
separated using any conventional separation methods. The resulting pure diastereomeric
esters or amides can then be hydrolyzed to yield the corresponding pure R or S isomers.
The hydrolysis reaction can be carried out using conventional known methods to
hydrolyze an ester or an amide without racemization.

30

All of the compounds of formula I which include the compounds set forth in the Examples, activated glucokinase *in vitro* by the procedure of Example A. In this manner, they increase the flux of glucose metabolism which causes increased insulin secretion. Therefore, the compounds of formula I are glucokinase activators useful for increasing insulin secretion.

On the basis of their capability of activating glucokinase, the compounds of above formula I can be used as medicaments for the treatment of type II diabetes. Therefore, as mentioned earlier, medicaments containing a compound of formula I are also an object of the present invention, as is a process for the manufacture of such medicaments, which process comprises bringing one or more compounds of formula I and, if desired, one or more other therapeutically valuable substances into a galenical administration form, e.g. by combining a compound of formula I with a pharmaceutically acceptable carrier and/or adjuvant.

The pharmaceutical compositions may be administered orally, for example in the form of tablets, coated tablets, dragées, hard or soft gelatine capsules, solutions, emulsions or suspensions. Administration can also be carried out rectally, for example using suppositories; locally or percutaneously, for example using ointments, creams, gels or solutions; or parenterally, e.g. intravenously, intramuscularly, subcutaneously, intrathecally or transdermally, using for example injectable solutions. Furthermore, administration can be carried out sublingually or as an aerosol, for example in the form of a spray. For the preparation of tablets, coated tablets, dragées or hard gelatine capsules the compounds of the present invention may be admixed with pharmaceutically inert, inorganic or organic excipients. Examples of suitable excipients for tablets, dragées or hard gelatine capsules include lactose, maize starch or derivatives thereof, talc or stearic acid or salts thereof. Suitable excipients for use with soft gelatine capsules include for example vegetable oils, waxes, fats, semi-solid or liquid polyols etc.; according to the nature of the active ingredients it may however be the case that no excipient is needed at all for soft gelatine capsules. For the preparation of solutions and syrups, excipients which may be used include for example water, polyols, saccharose, invert sugar and glucose. For injectable solutions, excipients which may be used include for example

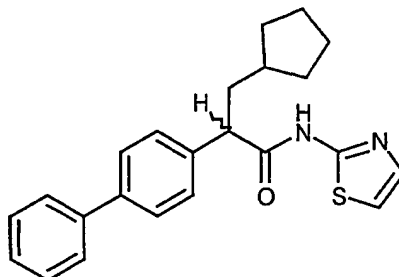
water, alcohols, polyols, glycerine, and vegetable oils. For suppositories, and local or percutaneous application, excipients which may be used include for example natural or hardened oils, waxes, fats and semi-solid or liquid polyols. The pharmaceutical compositions may also contain preserving agents, solubilising agents, stabilising agents, wetting agents, emulsifiers, sweeteners, colorants, odorants, salts for the variation of osmotic pressure, buffers, coating agents or antioxidants. As mentioned earlier, they may also contain other therapeutically valuable agents. It is a prerequisite that all adjuvants used in the manufacture of the preparations are non-toxic.

Preferred forms of use are intravenous, intramuscular or oral administration, most preferred is oral administration. The dosages in which the compounds of formula (I) are administered in effective amounts depend on the nature of the specific active ingredient, the age and the requirements of the patient and the mode of application. In general, dosages of about 1-100 mg/kg body weight per day come into consideration.

This invention will be better understood from the following examples, which are for purposes of illustration and are not intended to limit the invention defined in the claims which follow thereafter.

Example 1

(A) 2-Biphenyl-4-yl-3-cyclopentyl-N-thiazol-2-yl-propionamide



5

A solution of diisopropylamine (6.93 mL, 49.5 mmol) in dry tetrahydrofuran (64 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (16 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (19.8 mL, 49.5 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then
10 treated dropwise with a solution of 4-biphenylacetic acid (5.00 g, 23.6 mmol) in a small amount of dry tetrahydrofuran. The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (4.96 g, 23.6 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C over a period of 15 h. The reaction
15 mixture was quenched with water (100 mL), and the reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous layer was acidified to pH=2 with concentrated hydrochloric acid and then extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1
20 hexanes/ethyl acetate) afforded 2-biphenyl-4-yl-3-cyclopentylpropionic acid (5.13 g, 74%) as a white solid: mp 131-133°C; FAB-HRMS *m/e* calcd for C₂₀H₂₂O₂ (M+H)⁺ 294.1620, found 294.1626.

A solution of 2-biphenyl-4-yl-3-cyclopentylpropionic acid (121.0 mg, 0.41 mmol),
25 benztotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (218.1 mg, 0.49 mmol), triethylamine (172 µL, 1.23 mmol), and 2-aminothiazole (45.3 mg, 0.45 mmol) in dry *N,N*-dimethylformamide (1 mL) was stirred at 25°C under nitrogen for 24

h. The reaction mixture was concentrated *in vacuo* to remove *N,N*-dimethylformamide. The resulting residue was diluted with ethyl acetate (100 mL). The organic layer was washed with a 10% aqueous hydrochloric acid solution (1 x 100 mL), water (1 x 100 mL), and a saturated aqueous sodium chloride solution (1 x 100 mL). The organic layer
5 was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 9/1 to 3/1 hexanes/ethyl acetate gradient elution) afforded 2-biphenyl-4-yl-3-cyclopentyl-N-thiazol-2-yl-propionamide (102.2 mg, 66%) as a white solid: mp 194-195°C; EI-HRMS *m/e* calcd for C₂₃H₂₄N₂OS (M⁺) 376.1609, found 376.1612.

10

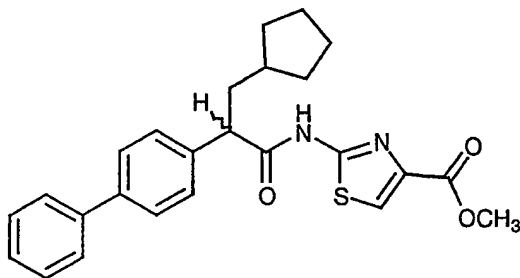
(B) In an analogous manner, there were obtained:

(a) From 2-biphenyl-4-yl-3-cyclopentylpropionic acid and methyl 2-amino-4-thiazoleacetate: [2-(2-Biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazol-4-yl]-acetic acid methyl ester as a white foam: mp 57-58°C; FAB-HRMS *m/e* calcd for C₂₆H₂₈N₂O₃S (M+H)⁺ 449.1899, found 449.1897.
15

(b) From 2-biphenyl-4-yl-3-cyclopentylpropionic acid and ethyl 2-amino-4-thiazoleglyoxylate: [2-(2-Biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazol-4-yl]-oxo-acetic acid ethyl ester as a yellow glass: mp 87-88°C; FAB-HRMS *m/e* calcd for C₂₇H₂₈N₂O₄S (M+H)⁺ 477.1848, found 477.1842.
20

(c) From 2-biphenyl-4-yl-3-cyclopentylpropionic acid and ethyl 2-amino-4-thiazoleacetate: [2-(2-Biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazol-4-yl]-acetic acid ethyl ester as a white foam: mp 78-80°C; FAB-HRMS *m/e* calcd for C₂₇H₃₀N₂O₃S (M+H)⁺ 463.2055, found 463.2052.
25

(d) From 2-biphenyl-4-yl-3-cyclopentylpropionic acid and 2-amino-thiazole-4-carboxylic acid ethyl ester: 2-(2-Biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazole-4-carboxylic acid ethyl ester as a white solid: mp 81-84°C; FAB-HRMS *m/e* calcd for C₂₆H₂₈N₂O₃S (M+H)⁺ 449.1899, found 449.1885.
30

Example 2**2-(2-Biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazole-4-carboxylic acid methyl ester**

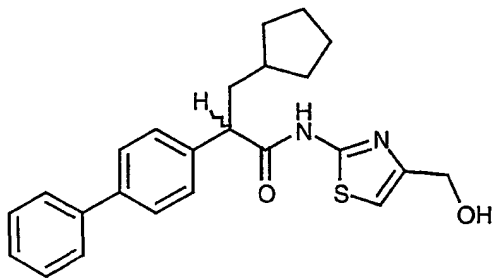
5

A solution of 2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazole-4-carboxylic acid ethyl ester (prepared in Example 1B-d, 200 mg, 0.45 mmol) in methanol (4 mL) was treated with concentrated sulfuric acid (2 drops). The reaction mixture was heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The resulting residue was partitioned between water and ethyl acetate. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1 hexanes/ethyl acetate) afforded 2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazole-4-carboxylic acid methyl ester (80 mg, 41%) as a white solid: mp 98-101°C; FAB-HRMS *m/e* calcd for C₂₅H₂₆N₂O₃S (M+H)⁺ 435.1743, found 435.1752.

15

Example 3**(A) 2-Biphenyl-4-yl-3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-propionamide**

20



A solution of 2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazole-4-carboxylic acid ethyl ester (prepared in Example 1B-d, 150 mg, 0.33 mmol) in diethyl ether (3 mL)

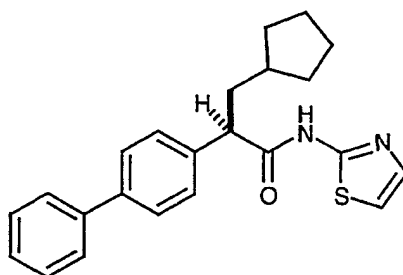
at 0°C under nitrogen was slowly treated with lithium aluminum hydride powder (16 mg, 0.44 mmol). The resulting reaction mixture continued to stir at 0°C and was then allowed to gradually warm to 25°C. The reaction mixture was then stirred at 25°C over a period of 64 h. The reaction mixture was slowly quenched by the dropwise addition of water (5 mL). The resulting reaction mixture was partitioned between water and ethyl acetate, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (1 x 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/2 hexanes/ethyl acetate) afforded 2-biphenyl-4-yl-3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-propionamide (65 mg, 48%) as a white solid: mp 102-104°C; EI-HRMS m/e calcd for C₂₄H₂₆N₂O₂S (M⁺) 406.1715, found 406.1711.

(B) In an analogous manner, there was obtained:

(a) From [2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazol-4-yl]-acetic acid ethyl ester: 2-Biphenyl-4-yl-3-cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-propionamide as a clear glass: mp 58-59°C; EI-HRMS m/e calcd for C₂₅H₂₈N₂O₂S (M⁺) 420.1872, found 420.1862.

Example 4

(2R)-2-Biphenyl-4-yl-3-cyclopentyl-N-thiazol-2-yl-propionamide

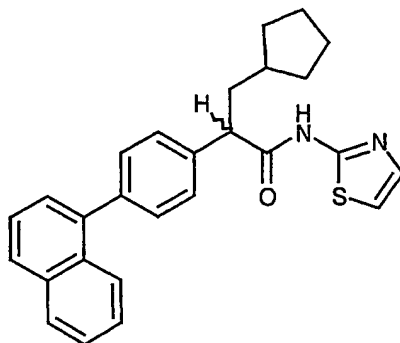


A solution of 2-biphenyl-4-yl-3-cyclopentylpropionic acid (prepared in Example 1A, 1.12 g, 3.80 mmol) in dry tetrahydrofuran (36 mL) under nitrogen was cooled to -78°C and then treated with triethylamine (606 mL, 4.35 mmol). The reaction mixture was stirred at -78°C for 15 min and then treated dropwise with trimethylacetyl chloride (491 mL, 3.98

mmol). The resulting reaction mixture was stirred at -78°C for 15 min, at which time, the cooling bath was removed, and the reaction mixture was allowed to warm to 25°C where it was stirred for 45 min. At this time, the reaction mixture was cooled back to -78°C for the addition of the chiral auxiliary. Into a separate reaction flask, a solution of (4S)-(-)-4-isopropyl-2-oxazolidinone (467.9 mg, 3.62 mmol) in dry tetrahydrofuran (18 mL) under nitrogen was cooled to -78°C and then treated with a 2.5M solution of *n*-butyllithium in hexanes (1.6 mL, 3.80 mmol). After complete addition of the *n*-butyllithium, the reaction mixture was allowed to warm to 25°C where it was stirred for 1 h. This cloudy white solution was then added dropwise by syringe to the previously cooled (-78°C) pivalate solution. The resulting reaction mixture was stirred at -78°C for 1 h and then allowed to gradually warm to 25°C. The reaction mixture was stirred at 25°C for 15 h. The resulting reaction mixture was quenched with a saturated aqueous sodium bisulfite solution and concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous residue was diluted with ethyl acetate (150 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 19/1 to 17/3 hexanes/ethyl acetate gradient elution) afforded the higher R_f product 3-{2(S)-biphenyl-4-yl-3-cyclopentyl-propionyl}-4(S)-isopropyl-oxazolidin-2-one (679.2 mg, 92%) as a yellow oil: EI-HRMS *m/e* calcd for C₂₆H₃₁NO₃ (M⁺) 405.2304, found 405.2310; and the lower R_f product 3-{2(R)-biphenyl-4-yl-3-cyclopentyl-propionyl}-4(S)-isopropyl-oxazolidin-2-one (127.4 mg, 17%) as a yellow oil: EI-HRMS *m/e* calcd for C₂₆H₃₁NO₃ (M⁺) 405.2304, found 405.2313.

A solution of 3-{2(R)-biphenyl-4-yl-3-cyclopentyl-propionyl}-4(S)-isopropyl-oxazolidin-2-one (127.4 mg, 0.31 mmol) in tetrahydrofuran (1.3 mL) and water (300 µL) was cooled to 0°C and then sequentially treated with a 30% aqueous hydrogen peroxide solution (39 µL, 1.25 mmol) and an 0.8M aqueous lithium hydroxide solution (628 µL, 0.50 mmol). The reaction mixture was allowed to warm to 25°C where it was stirred for 7 h. At this time, the reaction mixture was treated with solution of sodium sulfite (158.4 mg, 1.26 mmol) in water (952 µL). The reaction mixture was stirred at 0°C for 30 min

- and then concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous layer was extracted with diethyl ether (1 x 100 mL). The aqueous layer was then acidified to pH=1 with a 10% aqueous hydrochloric acid solution and extracted with ethyl acetate (1 x 100 mL). The organic extract was washed with water, dried over sodium sulfate,
- 5 filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 2(R)-biphenyl-4-yl-3-cyclopentylpropionic acid (43 mg, 46%) as a white solid: mp 136-137°C; EI-HRMS *m/e* calcd for C₂₀H₂₂O₂ (M⁺) 294.1620, found 294.1618.
- 10 A solution of 2(R)-biphenyl-4-yl-3-cyclopentylpropionic acid (36.9 mg, 0.13 mmol), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (52.3 mg, 0.14 mmol), *N,N*-diisopropylethylamine (66 µL, 0.38 mmol), and 2-aminothiazole (25.1 mg, 0.25 mmol) in dry *N,N*-dimethylformamide (627 µL) was stirred at 25°C under nitrogen for 13 h. The reaction mixture was concentrated *in vacuo* to remove the *N,N*-
- 15 dimethylformamide. The resulting residue was diluted with ethyl acetate (100 mL). The organic layer was washed with a 10% aqueous hydrochloric acid solution (1 x 100 mL), a saturated aqueous sodium bicarbonate solution (1 x 100 mL), and a saturated aqueous sodium chloride solution (1 x 100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230
- 20 mesh, 3/1 hexanes/ethyl acetate) afforded (2R)-2-biphenyl-4-yl-3-cyclopentyl-*N*-thiazol-2-yl-propionamide (29.4 mg, 62%) as a white foam: mp 132-134°C; FAB-HRMS *m/e* calcd for C₂₃H₂₄N₂OS (M+H)⁺ 377.1687, found 377.1696.

Example 5**(A) 3-Cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-N-thiazol-2-yl-propionamide**

5

A solution of diisopropylamine (17.1 mL, 122.21 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (12.2 mL, 122.21 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-iodophenylacetic acid (15.25 g, 58.19 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (13.45 g, 64.02 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 42 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran and then quenched with a 10% aqueous hydrochloric acid solution (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.97 g, 70%) as a cream solid: mp 121-122°C; EI-HRMS *m/e* calcd for C₁₄H₁₇IO₂ (M⁺) 344.0273, found 344.0275.

25 A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.00 g, 37.77 mmol) in methanol (94 mL) was treated slowly with concentrated sulfuric acid (5 drops). The

resulting reaction mixture was heated under reflux for 67 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (13.18 g, 97%) as a yellow semi-solid: EI-HRMS m/e calcd for C₁₅H₁₉IO₂ (M⁺) 358.0430, found 358.0434.

A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (3.87 g, 10.81 mmol), 1-naphthaleneboronic acid (2.79 g, 16.22 mmol), triethylamine (4.5 mL, 32.44 mmol), palladium (II) acetate (72.8 mg, 0.324 mmol), and tri-*o*-tolylphosphine (204.1 mg, 0.670 mmol) in dry *N,N*-dimethylformamide (43 mL) was heated at 100°C under nitrogen for 1 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove *N,N*-dimethylformamide. The residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL) and water (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid methyl ester (3.51 g, 90%) as a yellow oil: EI-HRMS m/e calcd for C₂₅H₂₆O₂ (M⁺) 358.1933, found 358.1930.

A solution of 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid methyl ester (3.32 g, 9.26 mmol) in tetrahydrofuran (12 mL) was treated with a 0.8M aqueous lithium hydroxide solution (12 mL). The resulting reaction mixture was stirred at 25°C for 24 h, at which time, thin layer chromatography indicated the presence of starting material. The reaction mixture was then heated at 80°C for 18 h. The reaction mixture was then allowed to cool to 25°C and concentrated *in vacuo* to remove tetrahydrofuran. The residue was acidified to pH=2 with a 10% aqueous hydrochloric acid solution and then extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck

Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid (1.74 g, 55%) as a white foam: mp 63-64°C; EI-HRMS m/e calcd for $C_{24}H_{24}O_2$ (M^+) 344.1776, found 344.1770.

- 5 A solution of 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid (100 mg, 0.29 mmol) in dry *N,N*-dimethylformamide (2 mL) was treated with *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (110 mg, 0.29 mmol), *N,N*-diisopropylethylamine (61 μ L, 0.35 mmol), and 2-aminothiazole (45 mg, 0.44 mmol). The reaction mixture was stirred at 25°C under nitrogen for 15 h. The reaction mixture
10 was poured into a mixture of water and ethyl acetate (1:1), and the layers were separated. The organic layer was washed with a 1N aqueous hydrochloric acid solution and a saturated aqueous sodium chloride solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 2/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-*N*-thiazol-2-yl-propionamide (92 mg, 74%) as a white foam: mp
15 202-204°C; FAB-HRMS m/e calcd for $C_{27}H_{26}N_2OS$ ($M+H$)⁺ 427.1844, found 427.1837.

(B) In an analogous manner, there were obtained:

- (a) From 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid and methyl 2-amino-4-thiazoleacetate:
20 {2-[3-Cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid methyl ester as a white foam: mp 65-69°C; EI-HRMS m/e calcd for $C_{30}H_{30}N_2O_3S$ (M^+) 498.1977, found 498.1982.

- (b) From 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid and ethyl 2-amino-4-thiazoleacetate:
25 {2-[3-Cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester as a white foam: mp 63-68°C; EI-HRMS m/e calcd for $C_{31}H_{32}N_2O_3S$ (M^+) 512.2134, found 512.2136.

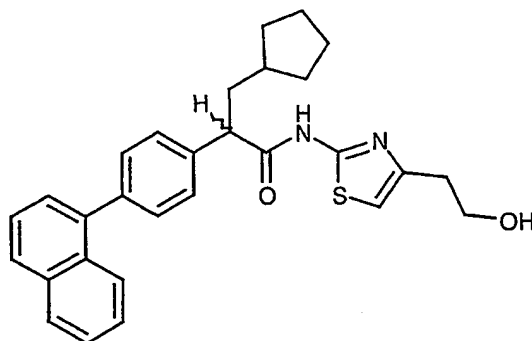
- (c) From 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid and 2-aminothiazole-4-carboxylic acid methyl ester: 2-[3-Cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-
30 thiazole-4-carboxylic acid methyl ester: 2-[3-Cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-

propionylamino]-thiazole-4-carboxylic acid methyl ester as a white foam: mp 103-107°C; EI-HRMS m/e calcd for C₂₉H₂₈N₂O₃S (M⁺) 484.1821, found 484.1825.

- (d) From 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid and 2-amino-4-(hydroxymethyl)thiazole hydrochloride: 3-Cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-naphthalen-1-yl-phenyl)-propionamide as a white foam: mp 90-93°C; EI-HRMS m/e calcd for C₂₈H₂₈N₂O₂S (M⁺) 456.1872, found 456.1867.

Example 6

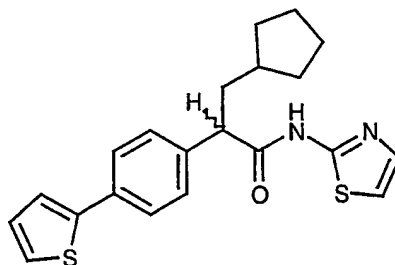
- 10 **3-Cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-2-(4-naphthalen-1-yl-phenyl)-propionamide**



- 15 A solution of {2-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester (prepared in Example 5B-b, 60 mg, 0.117 mmol) in diethyl ether (1 mL) was cooled to 0°C and then slowly treated with lithium aluminum hydride powder (6.7 mg, 0.176 mmol). The reaction mixture was stirred at 0°C for 30 min, at which time, thin layer chromatography showed the absence of starting material. The reaction mixture was slowly quenched by the dropwise addition of a saturated aqueous sodium bicarbonate solution (2 mL). The resulting reaction mixture was treated with ethyl acetate (2 mL) and allowed to stir at 25°C for 15 h. The two-phase reaction mixture was then partitioned between water (20 mL) and ethyl acetate (20 mL), and the layers were separated. The aqueous layer was further extracted with ethyl acetate (1 x 20 mL).
- 20 The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/2
- 25

hexanes/ethyl acetate) afforded 3-cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-2-(4-naphthalen-1-yl-phenyl)-propionamide (19 mg, 34%) as a yellow foam: mp 84-87°C; EI-HRMS m/e calcd for C₂₉H₃₀N₂O₂S (M⁺) 470.2028, found 470.2020.

5

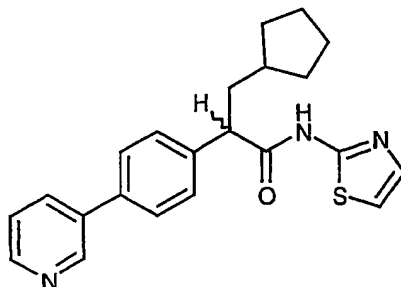
Example 7**3-Cyclopentyl-N-thiazol-2-yl-2-(4-thiophen-2-yl-phenyl)-propionamide**

- 10 A solution of diisopropylamine (7.7 mL, 54.88 mmol) in dry tetrahydrofuran (23 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (22.0 mL, 54.88 mmol). The reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-bromophenylacetic acid (5.62 g, 26.13 mmol) in dry
- 15 tetrahydrofuran (23 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (10 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 1 h, at which time, a solution of iodomethylcyclopentane (5.76 g, 27.44 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 24 h. The reaction mixture was quenched with
- 20 water and then concentrated *in vacuo* to remove tetrahydrofuran. The aqueous residue was acidified using a 10% aqueous hydrochloric acid solution. The resulting aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 2-(4-bromo-
- 25 phenyl)-3-cyclopentyl-propionic acid (3.88 g, 50%) as a light yellow solid: mp 91-93°C; EI-HRMS m/e calcd for C₁₄H₁₇BrO₂ (M⁺) 296.0412, found 296.0417.

A solution of 2-(4-bromo-phenyl)-3-cyclopentyl-propionic acid (1.01 g, 3.39 mmol) in methylene chloride (8.5 mL) was treated with dry *N,N*-dimethylformamide (2 drops). The reaction mixture was cooled to 0°C and then treated with oxalyl chloride (3 mL, 33.98 mmol). The reaction mixture was stirred at 0°C for 10 min and then stirred at 25°C for 15 h. The reaction mixture was concentrated *in vacuo*. The resulting yellow oil was dissolved in a small amount of methylene chloride and slowly added to a cooled solution (0°C) of 2-aminothiazole (680.6 mg, 6.79 mmol) and *N,N*-diisopropylethylamine (1.2 mL, 6.79 mmol) in methylene chloride (17 mL). The resulting reaction mixture was stirred at 0°C for 10 min and then at 25°C for 15 h. The reaction mixture was concentrated *in vacuo* to remove methylene chloride. The resulting residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a 10% aqueous hydrochloric acid solution (2 x 100 mL), a saturated aqueous sodium bicarbonate solution (2 x 100 mL), and a saturated aqueous sodium chloride solution (1 x 100 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 2-(4-bromo-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (1.23 g, 95%) as an orange solid which was used in subsequent reactions without further purification. An analytical sample was recrystallized from ethyl acetate to provide a cream solid: mp 201-202°C; EI-HRMS *m/e* calcd for C₁₇H₁₉BrN₂OS (M⁺) 378.0401, found 378.0405.

A mixture of 2-(4-bromo-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (102.5 mg, 0.27 mmol), tetrakis(triphenylphosphine)palladium(0) (15.6 mg, 0.014 mmol), 2-thiopheneboronic acid (69.2 mg, 0.54 mmol), and a 2M aqueous sodium carbonate solution (405 µL, 0.81 mmol) in 1,2-dimethoxyethane (9 mL) was heated under reflux for 24 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the catalyst. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-N-thiazol-2-yl-2-(4-thiophen-2-yl-phenyl)-propionamide (4.5 mg, 4%) as a yellow solid: mp 194°C (dec); EI-HRMS *m/e* calcd for C₂₁H₂₂N₂OS₂ (M⁺) 382.1174, found 382.1175.

Example 8
3-Cyclopentyl-2-(4-pyridin-3-yl-phenyl)-N-thiazol-2-yl-propionamide



- 5 A solution of diisopropylamine (17.1 mL, 122.21 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (12.2 mL, 122.21 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and
- 10 then treated dropwise with a solution of 4-iodophenylacetic acid (15.25 g, 58.19 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (13.45 g, 64.02 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was
- 15 allowed to warm to 25°C where it was stirred for 42 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran and then quenched with a 10% aqueous hydrochloric acid solution (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and
- 20 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.97 g, 70%) as a cream solid: mp 121-122°C; EI-HRMS *m/e* calcd for C₁₄H₁₇IO₂ (M⁺) 344.0273, found 344.0275.
- 25 A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.00 g, 37.77 mmol) in methanol (94 mL) was treated slowly with concentrated sulfuric acid (5 drops). The resulting reaction mixture was heated under reflux for 67 h. The reaction mixture was

allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100%
5 hexanes then 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (13.18 g, 97%) as a yellow semi-solid: EI-HRMS m/e calcd for C₁₅H₁₉IO₂ (M⁺) 358.0430, found 358.0434.

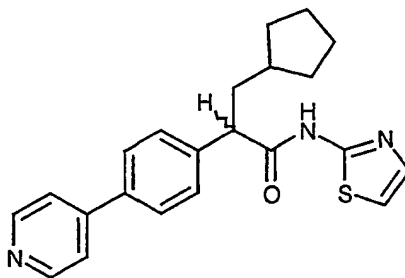
A slurry of dichlorobis(triphenylphosphine)palladium(II) (119 mg, 0.17 mmol) in 1,2-
10 dimethoxyethane (10 mL) was treated with 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (1.00 g, 2.79 mmol). The reaction slurry was stirred at 25°C for 10 min and then treated with a solution of pyridine-3-boronic acid (515 mg, 4.19 mmol) and a 2M aqueous sodium carbonate solution (2.8 mL, 5.58 mmol) in water (5 mL). The resulting reaction mixture was heated under reflux for 90 min. The reaction mixture was
15 allowed to cool to 25°C and then filtered to remove the catalyst. The filtrate was partitioned between water and methylene chloride, and the layers were separated. The aqueous layer was further extracted with methylene chloride (75 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate)
20 afforded 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionic acid methyl ester (800 mg, 92%) as a brown oil: EI-HRMS m/e calcd for C₂₀H₂₃NO₂ (M⁺) 309.1729, found 309.1728.

A solution of 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionic acid methyl ester (450
25 mg, 1.45 mmol) in tetrahydrofuran (5 mL) was treated with a 0.8M aqueous lithium hydroxide solution (2.18 mL, 1.74 mmol). The resulting reaction mixture was stirred at 25°C for 3 d. The reaction mixture was then partitioned between water (50 mL) and ethyl acetate (50 mL), and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were dried over
30 magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting solid was purified by precipitation from methylene chloride/ethyl acetate to afford 3-cyclopentyl-2-(4-

pyridin-3-yl-phenyl)-propionic acid (271 mg, 63%) as a white solid: mp 136-138°C; EI-HRMS m/e calcd for $C_{19}H_{21}NO_2$ (M^+) 295.1572, found 295.1572.

A solution of triphenylphosphine (160 mg, 0.61 mmol) in methylene chloride (4 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (109 mg, 0.61 mmol). The reaction mixture was stirred at 0°C for 30 min and then treated with 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionic acid (150 mg, 0.51 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminothiazole (112 mg, 1.12 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 100% diethyl ether then 1/1 diethyl ether/ethyl acetate then 1/3 diethyl ether/ethyl acetate) to afford 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-*N*-thiazol-2-yl-propionamide (15 mg, 8%) as a pale yellow foam: mp 48-52°C; EI-HRMS m/e calcd for $C_{22}H_{23}N_3OS$ (M^+) 377.1562, found 377.1564.

Example 9
3-Cyclopentyl-2-(4-pyridin-4-yl-phenyl)-*N*-thiazol-2-yl-propionamide



20

A solution of diisopropylamine (17.1 mL, 122.21 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (12.2 mL, 122.21 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-iodophenylacetic acid (15.25 g, 58.19 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18

mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (13.45 g, 64.02 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 42 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran and then quenched with a 10% aqueous hydrochloric acid solution (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.97 g, 70%) as a cream solid: mp 121-122°C; EI-HRMS *m/e* calcd for C₁₄H₁₇IO₂ (M⁺) 344.0273, found 344.0275.

A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.00 g, 37.77 mmol) in methanol (94 mL) was treated slowly with concentrated sulfuric acid (5 drops). The resulting reaction mixture was heated under reflux for 67 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (13.18 g, 97%) as a yellow semi-solid: EI-HRMS *m/e* calcd for C₁₅H₁₉IO₂ (M⁺) 358.0430, found 358.0434.

A slurry of dichlorobis(triphenylphosphine)palladium(II) (119 mg, 0.17 mmol) in 1,2-dimethoxyethane (10 mL) was treated with 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (1.00 g, 2.79 mmol). The reaction slurry was stirred at 25°C for 10 min and then treated with a solution of pyridine-4-boronic acid (515 mg, 4.19 mmol) and a 2M aqueous sodium carbonate solution (2.8 mL, 5.58 mmol) in water (5 mL). The resulting reaction mixture was heated under reflux for 8 h. The reaction mixture was allowed to cool to 25°C where it was stirred for 3 d. The reaction mixture was

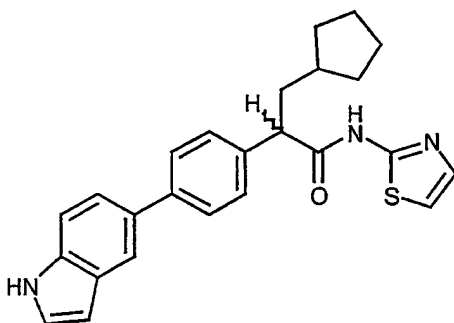
partitioned between water (75 mL) and methylene chloride (75 mL), and the layers were separated. The aqueous layer was further extracted with methylene chloride (75 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-propionic acid methyl ester (240 mg, 28%) as a brown oil that was used without further purification and characterization.

A solution of 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-propionic acid methyl ester (240 mg, 0.78 mmol) in tetrahydrofuran (3 mL) was treated with a 0.8M aqueous lithium hydroxide solution (1.45 mL, 1.16 mmol). The resulting reaction mixture was stirred at 25°C for 30 min and then heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C and then partitioned between water (100 mL) and ethyl acetate (70 mL). The layers were separated, and the aqueous layer was further extracted with ethyl acetate (1 x 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a yellow oil that solidified upon sitting. The solid was collected to afford 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-propionic acid (127 mg, 55%) as a yellow solid: mp 118-121°C; FAB-HRMS *m/e* calcd for C₁₉H₂₁NO₂ (M+H)⁺ 296.1650, found 296.1658.

A solution of triphenylphosphine (59 mg, 0.22 mmol) in methylene chloride (1 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (39 mg, 0.22 mmol). The reaction mixture was stirred at 0°C for 20 min and then treated with 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-propionic acid (55 mg, 0.19 mmol). The resulting reaction mixture was stirred at 0°C for 10 min and then allowed to warm to 25°C where it was stirred for 20 min. The reaction mixture was then treated with 2-aminothiazole (41 mg, 0.41 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 20/1 methylene chloride/methanol) to afford impure 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-*N*-thiazol-2-yl-propionamide as an orange foam. The impure foam was treated with a solution of hexanes/ethyl acetate (5 mL, 1:3), and a precipitate formed. The reaction mixture was placed in the freezer for 15 h, and the solid was collected by

filtration to afford 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-N-thiazol-2-yl-propionamide (26 mg, 37%) as a pale orange solid: mp 213-215°C; EI-HRMS *m/e* calcd for $C_{22}H_{23}N_3OS$ (M^+) 377.1562, found 377.1564.

5

Example 10**3-Cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-N-thiazol-2-yl-propionamide**

- 10 A solution of diisopropylamine (17.1 mL, 122.21 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (12.2 mL, 122.21 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-iodophenylacetic acid (15.25 g, 58.19 mmol) in
- 15 dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (13.45 g, 64.02 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 42 h. The reaction mixture was
- 20 concentrated *in vacuo* to remove tetrahydrofuran and then quenched with a 10% aqueous hydrochloric acid solution (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1
- 25 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.97 g,

70%) as a cream solid: mp 121-122°C; EI-HRMS m/e calcd for $C_{14}H_{17}IO_2$ (M^+) 344.0273, found 344.0275.

5 A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.00 g, 37.77 mmol) in methanol (94 mL) was treated slowly with concentrated sulfuric acid (5 drops). The resulting reaction mixture was heated under reflux for 67 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and
10 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (13.18 g, 97%) as a yellow semi-solid: EI-HRMS m/e calcd for $C_{15}H_{19}IO_2$ (M^+) 358.0430, found 358.0434.

15 A slurry of dichlorobis(triphenylphosphine)palladium(II) (119 mg, 0.17 mmol) in 1,2-dimethoxyethane (10 mL) was treated with 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (1.00 g, 2.79 mmol). The reaction slurry was stirred at 25°C for 10 min and then treated with a mixture of 5-indolylboronic acid (670 mg, 4.19 mmol) in water (5 mL) and a 2M aqueous sodium carbonate solution (2.8 mL, 5.58 mmol). The resulting
20 reaction mixture was heated under reflux for 2 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the catalyst. The filtrate was partitioned between water (50 mL) and methylene chloride (50 mL), and the layers were separated. The aqueous layer was further extracted with methylene chloride (50 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated
25 *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/2 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-propionic acid methyl ester (347 mg, 36%) as a light brown oil: EI-HRMS m/e calcd for $C_{23}H_{25}NO_2$ (M^+) 347.1885, found 347.1887.

30 A solution of 3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-propionic acid methyl ester (310 mg, 0.89 mmol) in tetrahydrofuran (2 mL) was treated with a 0.8M aqueous lithium

hydroxide solution (1.45 mL, 1.16 mmol). The resulting reaction mixture was stirred at 25°C for 39 h and then heated at 80°C for 4 h. The reaction mixture was then allowed to cool to 25°C where it was stirred for 3 d. The reaction mixture was then concentrated *in vacuo* to remove tetrahydrofuran. The resulting aqueous layer was extracted with
5 methylene chloride (2 x 40 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-propionic acid (170 mg, 58%) as a pale yellow foam: mp 62-65°C; FAB-HRMS *m/e* calcd for C₂₂H₂₃NO₂ (M+H)⁺ 333.1729, found 333.1731.

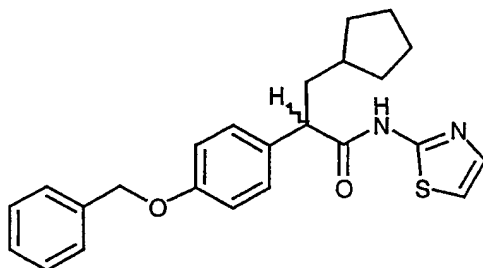
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A solution of triphenylphosphine (71 mg, 0.27 mmol) in methylene chloride (1.5 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (48 mg, 0.27 mmol). The reaction mixture was stirred at 0°C for 25 min and then treated with 3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-propionic acid (75 mg, 0.23 mmol). The
15 resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 30 min. The reaction mixture was then treated with 2-aminothiazole (50 mg, 0.50 mmol). The resulting reaction mixture was stirred at 25°C for 5 d. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 9/1 chloroform/methanol) to afford impure 3-
20 cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-N-thiazol-2-yl-propionamide. Repurification by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 hexanes/ethyl acetate) afforded pure 3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-N-thiazol-2-yl-propionamide (8 mg, 9%) as a white solid: mp 112-115°C; EI-HRMS *m/e* calcd for C₂₅H₂₅N₃OS (M⁺) 415.1718, found 415.1714.

25

Example 11

2-(4-Benzyloxy-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide



5 A mixture of (4-hydroxy-phenyl)-acetic acid methyl ester (5.0 g, 30.0 mmol) and potassium carbonate (5.0 g, 36.1 mmol) in acetone (10 mL) was treated with benzyl bromide (4.29 mL, 36.1 mmol). The reaction mixture was then heated at 90°C for 6 h. At this time, the potassium carbonate was removed by filtration. The filtrate was
10 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 95/5 hexanes/ethyl acetate) afforded (4-benzyloxy-phenyl)-acetic acid methyl ester (7.1 g, 92.1%) as a clear oil: EI-HRMS *m/e* calcd for C₁₆H₁₆O₃ (M⁺) 256.1099 found 256.1103.

A solution of freshly prepared lithium diisopropylamide (23 mL of a 0.31M stock
15 solution, 7.13 mmol) was cooled to -78°C and then treated with a solution of (4-benzyloxy-phenyl)-acetic acid methyl ester (1.66 g, 6.48 mmol) in tetrahydrofuran/1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (16.1 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (1.50 g, 7.13 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-
20 pyrimidinone (2 mL). The reaction mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 48 h. At this time, the reaction mixture was quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (10 mL). This mixture was poured into water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with a
25 saturated aqueous lithium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 98/2 hexanes/ethyl acetate) afforded 2-(4-benzyloxy-phenyl)-3-cyclopentyl-

propionic acid methyl ester (1.90 g, 86.6%) as a white wax: mp 55-57°C; EI-HRMS m/e calcd for $C_{22}H_{26}O_3$ (M^+) 338.1881 found 228.1878.

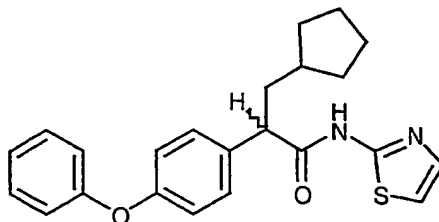
5 A solution of 2-(4-benzyloxy-phenyl)-3-cyclopentyl-propionic acid methyl ester (1.38 g, 4.08 mmol) in tetrahydrofuran/water/methanol (10.2 mL, 3:1:1) was treated with a 2N aqueous sodium hydroxide solution (3.06 mL, 6.12 mmol). The reaction was stirred at 25°C for 16 h. At this time, an additional amount of the 2N aqueous sodium hydroxide solution (3.06 mL, 6.12 mmol) was added. The reaction was stirred at 25°C for an additional 24 h. At this time, the reaction mixture was poured into water and extracted
10 into methylene chloride. The layers were separated. The aqueous layer was acidified to pH=1 with a 1N aqueous hydrochloric acid solution and was then extracted with a solution of methylene chloride/methanol (90/10). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 2-(4-
15 benzyloxy-phenyl)-3-cyclopentyl-propionic acid (0.79 g, 60.2%) as a white solid: mp 112-114°C.

A solution of 2-(4-benzyloxy-phenyl)-3-cyclopentyl-propionic acid (0.15 g, 0.46 mmol) in methylene chloride (4.6 mL) was cooled to 0°C and then treated with a 2.0M solution
20 of oxalyl chloride in methylene chloride (0.25 mL, 0.50 mmol) and a few drops of *N,N*-dimethylformamide. The reaction mixture was stirred at 0°C for 10 min and at 25°C for 30 min. The reaction mixture was then treated with a solution of 2-aminothiazole (0.10 g, 1.01 mmol) and *N,N*-diisopropylethylamine (0.19 mL, 1.10 mmol) in tetrahydrofuran (2.3 mL). The reaction mixture was stirred at 25°C for 18 h. At this time, the reaction
25 was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh 80/20 hexanes/ethyl acetate) afforded 2-(4-benzyloxy-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (119.4 mg, 63.5%) as a white solid: mp 48-50°C; EI-HRMS m/e calcd for $C_{24}H_{26}N_2O_2S$ (M^+) 406.1715, found 406.1716.

30

Example 12

(A) 3-Cyclopentyl-2-(4-phenoxy-phenyl)-N-thiazol-2-yl-propionamide



5

A solution of diisopropylamine (2.52 mL, 19.3 mmol) in tetrahydrofuran (50 mL) was cooled to -78°C under a nitrogen atmosphere and then treated with a 2.5M solution of *n*-butyllithium in hexanes (7.7 mL, 19.3 mmol). The reaction mixture was stirred at -78°C for 15 min and then slowly treated with a solution of 4-phenoxyphenylacetic acid (2.00 g, 8.8 mmol) in tetrahydrofuran (12 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (4 mL) via cannulation. The resulting bright yellow solution was allowed to stir for 1 h at -78°C . After this time, the reaction mixture was treated with a solution of iodomethylcyclopentane (2.02 g, 9.6 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1 mL) via cannulation. The resulting reaction mixture was stirred for 1 h at -78°C and then allowed to warm to 25°C where it was stirred for 14 h. The reaction was then acidified to pH=2 by the dropwise addition of a 1N aqueous hydrochloric acid solution and then extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate plus 1% acetic acid) afforded 3-cyclopentyl-2-(4-phenoxy-phenyl)propionic acid (2.49 g, 91%) as a white foam: EI-HRMS *m/e* calcd for $\text{C}_{20}\text{H}_{22}\text{O}_3$ (M^+) 310.1568, found 310.1568.

A solution of 3-cyclopentyl-2-(4-phenoxy-phenyl)-propionic acid (50 mg, 0.16 mmol), benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (106 mg, 0.24 mmol), and 2-aminothiazole (21 mg, 0.24 mmol) in methylene chloride (10 mL) at 25°C was treated with triethylamine (0.067 mL, 0.48 mmol). The reaction mixture was then stirred at 25°C for 14 h. After this time, the reaction mixture was diluted with water

25

(10 mL) and then extracted with methylene chloride (3 x 10 mL). The combined organic extracts were then washed with water (1 x 10 mL), a 1N aqueous sodium hydroxide solution (1 x 10 mL), and a 1N aqueous hydrochloric acid solution (1 x 10 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo*.

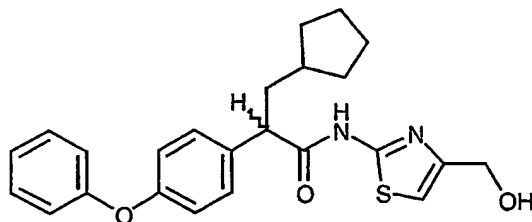
- 5 Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-phenoxy-phenyl)-N-thiazol-2-yl-propionamide (48 mg, 76%) as an off-white solid: mp 154.9-155.1°C; EI-HRMS *m/e* calcd for $C_{23}H_{24}O_2N_2S$ (M^+) 392.1558, found 392.1546.

- 10 (B) In an analogous manner, there was obtained:

(a) From 3-cyclopentyl-2-(4-phenoxy-phenyl)propionic acid and 2-aminothiazol-4-yl-acetic acid ethyl ester: {2-[3-Cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester as a white foam: FAB-HRMS *m/e* calcd for $C_{27}H_{30}N_2O_4S$ ($M+H$)⁺ 479.2004, found 479.2001.

15

Example 13
3-Cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-phenoxy-phenyl)-propionamide



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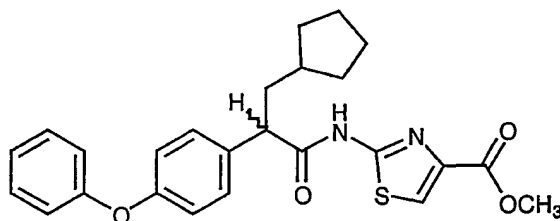
- A solution of 3-cyclopentyl-2-(4-phenoxy-phenyl)-propionic acid (prepared in Example 12A, 767 mg, 2.47 mmol) in methylene chloride (20 mL) at 25°C was treated with 2-amino-thiazole-4-carboxylic acid ethyl ester (553 mg, 3.21 mmol), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (1.64 g, 3.71 mmol), and triethylamine (1 mL, 7.41 mmol). The resulting reaction mixture was stirred at 25°C for 16 h. The reaction mixture was then diluted with water (10 mL) and then extracted with methylene chloride (3 x 15 mL). The combined organic extracts were washed with a 1N aqueous sodium hydroxide solution (1 x 10 mL), a 1N aqueous hydrochloric acid solution
- 25

(1 x 10 mL), and a saturated aqueous sodium chloride solution (1 x 10 mL). The organic layer was then dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (564 mg, 49%) as a white foam: FAB-HRMS *m/e* calcd for C₂₆H₂₈N₂O₄S (M+H)⁺ 465.1848, found 465.1831.

A solution of 2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (100 mg, 0.22 mmol) in diethyl ether (10 mL) was cooled to 0°C and then treated with lithium aluminum hydride (13 mg, 0.32 mmol). The reaction mixture was slowly warmed to 25°C where it was stirred for 16 h. After this time, the reaction mixture was slowly diluted with water (5 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-phenoxy-phenyl)-propionamide (50 mg, 55%) as a white solid: mp 83.7-87°C; EI-HRMS *m/e* calcd for C₂₄H₂₆N₂O₃S (M⁺) 422.1664, found 422.1674.

Example 14

20 2-[3-Cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester

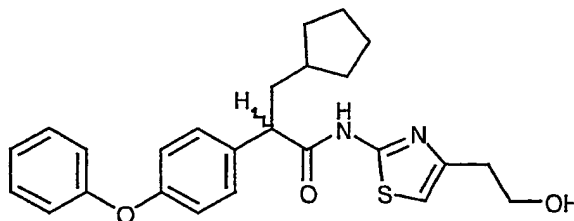


25 A solution of 2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazole-4-carboxylic acid ethyl ester (prepared in Example 13, 300 mg, 0.65 mmol) in ethanol (20 mL) at 25°C was treated with a solution of potassium hydroxide (109 mg, 1.94 mmol) in water (6 mL). This light yellow solution was stirred at 25°C for 2 h and then concentrated *in vacuo* to remove ethanol. The resulting aqueous solution was acidified to

pH=2 with a 1N aqueous hydrochloric acid solution and then extracted with methylene chloride (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 20/80 hexanes/ethyl acetate plus 1% acetic acid) afforded 2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazole-4-carboxylic acid (226 mg, 80%) as a white solid: mp >200°C; FAB-HRMS *m/e* calcd for C₂₄H₂₄N₂O₄S (M+H)⁺ 437.1535, found 437.1534.

A solution of 2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazole-4-carboxylic acid (100 mg, 0.23 mmol) in methanol (10 mL) was treated with concentrated hydrochloric acid (1 mL) and then heated under reflux for 16 h. At this time, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (10 mL) and then washed with water (5 mL). The aqueous layer was further extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester (40 mg, 39%) as a white foam: EI-HRMS *m/e* calcd for C₂₅H₂₆N₂O₄S (M⁺) 450.1613, found 450.1615.

Example 15
3-Cyclopentyl-N-[4-(2-hydroxy-ethyl)-thiazol-2-yl]-2-(4-phenoxy-phenyl)-propionamide

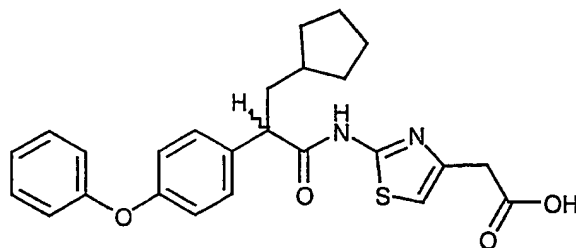


A solution of {2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester (prepared in Example 12B-a, 86 mg, 0.18 mmol) in diethyl ether (5 mL) was cooled to 0°C and then treated with lithium aluminum hydride (10 mg, 0.27 mmol). The reaction mixture was slowly warmed to 25°C where it was stirred for 16 h.

At this time, the reaction mixture was slowly diluted with water (5 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 3-cyclopentyl-N-[4-(2-hydroxy-ethyl)-thiazol-2-yl]-2-(4-phenoxy-phenyl)-propionamide (21 mg, 27%) as an off-white solid: FAB-HRMS *m/e* calcd for $C_{25}H_{28}N_2O_3S$ ($M+H$)⁺ 437.1899, found 437.1900.

Example 16

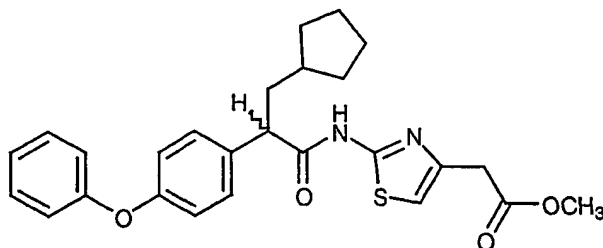
10 {2-[3-Cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid



A solution of {2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester (prepared in Example 12B-a, 276 mg, 0.58 mmol) in ethanol (20 mL) at 25°C was treated with a solution of potassium hydroxide (100 mg, 1.78 mmol) in water (6 mL). This light yellow solution was stirred at 25°C for 2 h and then concentrated *in vacuo* to remove ethanol. The resulting aqueous solution was acidified to pH=2 with a 1N aqueous hydrochloric acid solution and then extracted with methylene chloride (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 10/90 hexanes/ethyl acetate plus 1% acetic acid) afforded {2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid (222 mg, 80%) as a white foam: FAB-HRMS *m/e* calcd for $C_{25}H_{26}N_2O_4S$ ($M+H$)⁺ 451.1691, found 451.1686.

25

Example 17

{2-[3-Cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid methyl ester

5

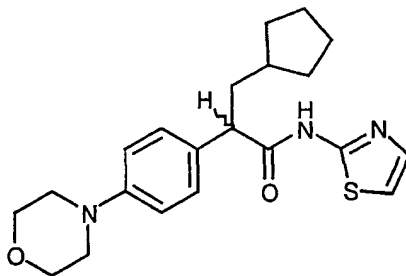
A solution of {2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid (prepared in Example 16, 80 mg, 0.18 mmol) in methanol (10 mL) was treated with concentrated hydrochloric acid (1 mL) and then heated under reflux for 16 h. At this time, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in ethyl acetate (10 mL) and then washed with water (5 mL). The aqueous layer was further extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded {2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid methyl ester (50 mg, 61%) as a yellow oil: EI-HRMS *m/e* calcd for C₂₆H₂₈N₂O₄S (M⁺) 464.1770, found 464.1769.

15

Example 18

3-Cyclopentyl-2-(4-morpholin-4-yl-phenyl)-N-thiazol-2-yl-propionamide

20



25

A mixture of 4-morpholinoacetophenone (4.61 g, 22 mmol), sulfur (2.16 g, 67 mmol), and morpholine (6 mL, 67 mmol) was heated at 80°C for 1h then heated under reflux for 18 h. The hot reaction mixture was poured into warm ethanol. Upon cooling to 25°C, a

precipitate formed. The precipitate was filtered to provide a tan solid (4.16 g). This crude tan solid was then treated with concentrated acetic acid (16 mL), concentrated sulfuric acid (2.4 mL), and water (3.6 mL). The resulting reaction mixture was heated under reflux for 4 h and then poured into water. The water was removed *in vacuo* to provide crude (4-morpholin-4-yl-phenyl)-acetic acid as a brown oil (8.20 g). This crude (4-morpholin-4-yl-phenyl)-acetic acid was dissolved in methanol (100 mL) and then slowly treated with concentrated sulfuric acid (1 mL). The reaction mixture was heated under reflux for 66 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with water (200 mL) and then treated with a 10% aqueous sodium hydroxide solution until pH=9. The aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 to 1/1 hexanes/ethyl acetate gradient elution) afforded (4-morpholin-4-yl-phenyl)-acetic acid methyl ester (2.22 g, 42% for 3 steps) as a yellow oil: EI-HRMS m/e calcd for C₁₃H₁₇NO₃ (M⁺) 235.1208, found 235.1214.

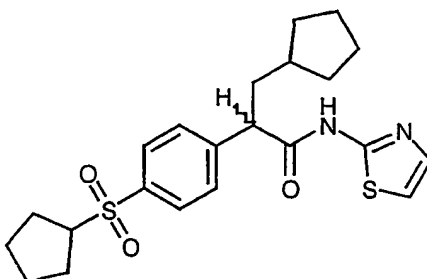
A solution of diisopropylamine (344 µL, 2.45 mmol) in dry tetrahydrofuran (2.9 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (981 µL, 2.45 mmol). The reaction mixture was stirred at -78°C for 15 min and then treated dropwise with a solution of (4-morpholin-4-yl-phenyl)-acetic acid methyl ester (549.9 mg, 2.34 mmol) in dry tetrahydrofuran (2 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1 mL). The resulting reaction mixture was allowed to stir at -78°C for 30 min, at which time, a solution of iodomethylcyclopentane (540.0 mg, 2.57 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was then allowed to warm to 25°C where it was stirred for 67 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The aqueous residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded

3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-propionic acid methyl ester (381.4 mg, 51%) as a white solid: mp 68-70°C; EI-HRMS m/e calcd for $C_{19}H_{27}NO_3$ (M^+) 317.1991, found 317.2001.

- 5 A solution of 3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-propionic acid methyl ester (210.8 mg, 0.66 mmol) in tetrahydrofuran (830 μ L) was treated with a 0.8M aqueous lithium hydroxide solution (1.2 mL). The reaction mixture was stirred at 25°C for 23 h and then concentrated *in vacuo* to remove tetrahydrofuran. The white residue was acidified to pH=2 with a 10% aqueous hydrochloric solution. The resulting aqueous
10 phase was extracted with ethyl acetate (2 x 75 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Trituration from hexanes/diethyl ether afforded 3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-propionic acid (173.7 mg, 86%) as a white solid: mp 145-147°C; EI-HRMS m/e calcd for $C_{18}H_{25}NO_3$ (M^+)
15 303.1834, found 303.1843.

- A solution of 3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-propionic acid (202.5 mg, 0.67 mmol) in dry *N,N*-dimethylformamide (3.3 mL) was treated with *N,N*-diisopropylethylamine (350 μ L, 2.00 mmol), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (303.8 mg, 0.80 mmol), and 2-aminothiazole
20 (133.7 mg, 1.34 mmol). The reaction mixture was stirred at 25°C under nitrogen for 15 h. The reaction mixture was then concentrated *in vacuo* to remove *N,N*-dimethylformamide. The residue was diluted with ethyl acetate (150 mL), and the organic phase was washed with a 10% aqueous hydrochloric acid solution (1 x 75 mL)
25 and a saturated aqueous sodium chloride solution (1 x 75 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-*N*-thiazol-2-yl-propionamide (87.5 mg, 34%) as a white solid: mp 244-246°C; EI-HRMS m/e calcd for $C_{21}H_{27}N_3O_2S$ (M^+) 385.1824, found 385.1832.

30

Example 19**(A) 2-(4-Cyclopentanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide**

5 A solution of freshly prepared lithium diisopropylamide (430.55 mL of a 0.3M stock solution, 129.16 mmol) was cooled to -78°C and then treated with a solution of (4-nitro-phenyl)-acetic acid ethyl ester (26.32 g, 125.83 mmol) in tetrahydrofuran/hexamethylphosphoramide (312.5 mL, 3:1). The resulting solution was
10 stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (27.75 g, 132.1 mmol) in hexamethylphosphoramide (27.75 mL). The mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 16 h. At this time, the reaction mixture was quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (250 mL). This
15 mixture was concentrated *in vacuo*, diluted with water (250 mL), and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were washed with a saturated aqueous lithium chloride solution (2 x 250 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 98/2 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid
20 ethyl ester (28.30 g, 77.2%) as a yellow oil: EI-HRMS *m/e* calcd for C₁₆H₂₁NO₄ (M⁺) 291.1470, found 291.1470.

A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (7.37 g, 25.3 mmol) in ethyl acetate (316 mL) was treated with 10% palladium on activated carbon
25 (500 g). The reaction mixture was shaken under 60 psi of hydrogen gas at 25°C for 18 h. The catalyst was then removed by filtration through a pad of celite and washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give 2-(4-amino-phenyl)-3-

cyclopentyl-propionic acid ethyl ester (3.52 g, 53.3%) as a yellow oil: EI-HRMS m/e calcd for $C_{16}H_{23}NO_2$ (M^+) 261.1727, found 261.1727.

A mixture of concentrated hydrochloric acid (0.47 mL) and ice (475 mg) was cooled to
5 0°C and then treated with 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester
(620 mg, 2.37 mmol). After 5 min, a solution of sodium nitrite (174 mg, 2.51 mmol) in
water (0.37 mL) was added to the reaction mixture. The resulting solution was stirred at
0°C for 5 min. At this time, the solution was added to a solution of cyclopentanethiol
(0.29 mL, 2.75 mmol) in water (0.45 mL) warmed to 45°C. The reaction was stirred at
10 45°C for 18 h. At this time, the reaction was diluted with water (100 mL) and extracted
with chloroform (3 x 50 mL). The combined organic extracts were dried over sodium
sulfate, filtered, and concentrated *in vacuo*. The crude brown oil (679 mg) was dissolved
in methylene chloride (9.80 mL), cooled to 0°C, and then treated with 3-
chloroperoxybenzoic acid (80-85% grade, 1.69 g, 9.79 mmol). The reaction mixture was
15 stirred at 25°C for 18 h. At this time, the reaction was diluted with methylene chloride
(100 mL). This solution was washed with a saturated aqueous sodium bisulfite solution
(1 x 100 mL), a saturated aqueous sodium chloride solution (1 x 100 mL), a saturated
aqueous sodium bicarbonate solution (1 x 100 mL), and a saturated aqueous sodium
chloride solution (1 x 100 mL). The organic layer was dried over sodium sulfate, filtered,
20 and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh,
80/20 hexanes/ethyl acetate) afforded 2-(4-cyclopentanesulfonyl-phenyl)-3-cyclopentyl-
propionic acid ethyl ester (164 mg, 18.3%) as a red oil: FAB-HRMS m/e calcd for
 $C_{21}H_{30}O_4S$ ($M+H$)⁺ 379.1925 found 379.1943.

25 A solution of 2-(4-cyclopentanesulfonyl-phenyl)-3-cyclopentyl-propionic acid ethyl ester
(160 mg, 0.42 mmol) in tetrahydrofuran/water/methanol (1.05 mL, 3:1:1) was treated
with a 1N aqueous lithium hydroxide solution (0.85 mL, 0.85 mmol). The reaction was
stirred at 25°C for 18 h. At this time, the reaction was diluted with chloroform (30 mL)
and water (50 mL), acidified to pH=1 with a 1N aqueous hydrochloric acid solution, and
30 extracted with a solution of chloroform/methanol (90/10, 3 x 50 mL). The combined
organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*.

Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 chloroform/methanol) afforded 2-(4-cyclopentanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (101.9 mg, 68.7%) as an off white solid: mp 165-167°C; FAB-HRMS m/e calcd for $C_{19}H_{26}O_4S$ ($M+H$)⁺ 351.1630 found 351.1646.

5

A solution of triphenylphosphine (106 mg, 0.40 mmol) and *N*-bromosuccinimide (82 mg, 0.45 mmol) in methylene chloride (1.35 mL) was cooled to 0°C and then treated with a solution of 2-(4-cyclopentanesulfonyl-phenyl)-3-cyclopentyl-propionic acid (94.8 mg, 0.27 mmol) in methylene chloride. The reaction mixture was stirred at 25°C for 45 min.

10 At this time, the reaction was treated with 2-aminothiazole (35 mg, 0.35 mmol) and pyridine (0.03 mL, 0.40 mmol). The reaction was stirred at 25°C for 18 h. The reaction was then diluted with water (100 mL) and extracted with chloroform (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 2-(4-cyclopentanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide (84 mg, 71.8%) as a light-orange solid: mp 180-182°C; EI-HRMS m/e calcd for $C_{22}H_{28}N_2O_3S_2$ (M^+) 432.1541 found 432.1543.

15

(B) In an analogous manner, there were obtained:

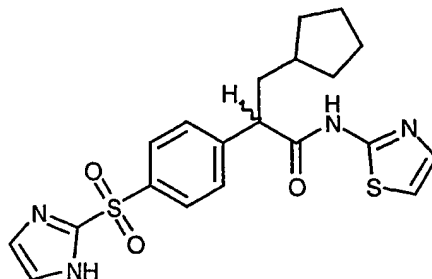
20 (a) From 2-(4-cyclohexanesulfonyl-phenyl)-3-cyclopentyl-propionic acid and 2-aminothiazole: 2-(4-Cyclohexanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide as an off-white solid: mp 220-222°C; EI-HRMS m/e calcd for $C_{23}H_{30}N_2O_3S_2$ (M^+) 446.1698 found 446.1700.

25 (b) From 2-(4-benzenesulfonyl-phenyl)-3-cyclopentyl-propionic acid and 2-aminothiazole: 2-(4-Benzenesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide as a yellow foam: mp 128-131°C; EI-HRMS m/e calcd for $C_{23}H_{24}N_2O_3S_2$ (M^+) 440.122, found 440.1222.

30

Example 20

3-Cyclopentyl-2-[4-(1H-imidazole-2-sulfonyl)-phenyl]-N-thiazol-2-yl-propionamide



5 A mixture of concentrated hydrochloric acid (0.49 mL) and ice (493 mg) was cooled to 0°C and then treated with 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (prepared in Example 19A, 716 mg, 2.74 mmol). After 5 min, a solution of sodium nitrite (200 mg, 2.90 mmol) in water (0.45 mL) was added to the reaction mixture. The

10 resulting solution was stirred at 0°C for 5 min. At this time, the solution was added to a solution of 1H-imidazole-2-thiol (318 mg, 1.16 mmol) in water (0.60 mL) warmed to 45°C. The reaction was stirred at 45°C for 4 h. At this time, the reaction was diluted with water (50 mL) and extracted with chloroform (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude

15 brown oil (683 mg) was dissolved in formic acid (5.72 mL, 99.71 mmol), cooled to 0°C, and then treated with a 30% aqueous hydrogen peroxide solution (3.82 mL, 9.11 mmol). This solution was stirred at 0°C for 1 h and at 25°C for 5 h. At this time, the reaction was quenched by the dropwise addition of a saturated aqueous sodium bisulfite solution. This solution was extracted with chloroform (3 x 50 mL). The combined organic extracts

20 were washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 70/30 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-[4-(1H-imidazole-2-sulfonyl)-phenyl]-propionic acid ethyl ester (222.4 mg, 21.5%) as a yellow oil: EI-HRMS *m/e* calcd for C₁₉H₂₄N₂O₄S (M⁺) 376.1456 found 376.1454.

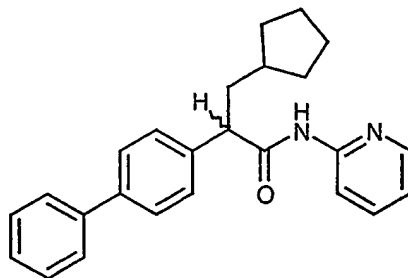
25

A mixture of 3-cyclopentyl-2-[4-(1H-imidazole-2-sulfonyl)-phenyl]-propionic acid ethyl ester (113.5 mg, 0.30 mmol) and 2-aminothiazole (45.3 mg, 0.45 mmol) in a solution of

magnesium methoxide in methanol (7.4 wt.%, 0.86 mL, 0.60 mmol) was heated at 110°C for 8 h. At this time, the reaction was cooled to 25°C, filtered through a plug of celite, and washed with ethyl acetate. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 75/25 hexanes/ethyl acetate) afforded the 3-cyclopentyl-2-[4-(1H-imidazole-2-sulfonyl)-phenyl]-N-thiazol-2-yl-propionamide (24.7 mg, 19%) as a tan solid: mp 249-251°C; EI-HRMS *m/e* calcd for C₂₀H₂₂N₄O₂S₂ (M⁺) 430.1133 found 430.1133.

Example 21

2-Biphenyl-4-yl-3-cyclopentyl-N-pyridin-2-yl-propionamide



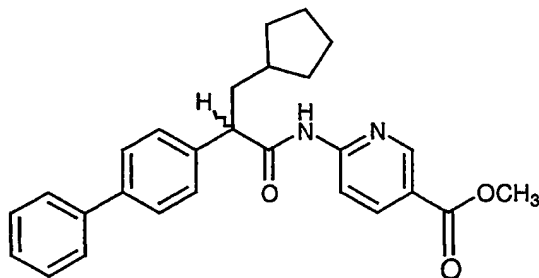
A solution of diisopropylamine (6.93 mL, 49.5 mmol) in dry tetrahydrofuran (64 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (16 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (19.8 mL, 49.5 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-biphenylacetic acid (5.00 g, 23.6 mmol) in a small amount of dry tetrahydrofuran. The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (4.96 g, 23.6 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C over a period of 15 h. The reaction mixture was quenched with water (100 mL), and the reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous layer was acidified to pH=2 with concentrated hydrochloric acid and then extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1

hexanes/ethyl acetate) afforded 2-biphenyl-4-yl-3-cyclopentylpropionic acid (5.13 g, 74%) as a white solid: mp 131-133°C; FAB-HRMS *m/e* calcd for C₂₀H₂₂O₂ (M+H)⁺ 294.1620, found 294.1626.

- 5 A solution of 2-biphenyl-4-yl-3-cyclopentylpropionic acid (300 mg, 1.02 mmol), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (386 mg, 1.02 mmol), *N,N*-diisopropylethylamine (220 µL, 1.22 mmol), and 2-aminopyridine (144 mg, 1.53 mmol) in dry *N,N*-dimethylformamide (5 mL) was stirred at 25°C under nitrogen for 15 h. The reaction mixture was partitioned between water and ethyl acetate, and the
10 layers were separated. The organic layer was washed with a 1N aqueous hydrochloric acid solution, water, and a saturated aqueous sodium chloride solution. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1 hexanes/ethyl acetate) afforded 2-biphenyl-4-yl-3-cyclopentyl-*N*-pyridin-2-yl-propionamide (79 mg, 21%) as a white
15 solid: mp 57-59°C; EI-HRMS *m/e* calcd for C₂₅H₂₆NO (M⁺) 370.2045, found 370.2049.

Example 22

6-(2-Biphenyl-4-yl-3-cyclopentyl-propionylamino)-nicotinic acid methyl ester

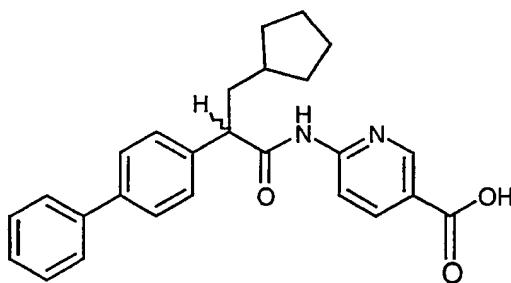


- A slurry of 2-biphenyl-4-yl-3-cyclopentylpropionic acid (prepared in Example 21, 1.25 g, 4.25 mmol) in methylene chloride (10 mL) was treated with dry *N,N*-dimethylformamide (5 drops). The reaction mixture was cooled to 0°C and then treated dropwise with oxalyl
25 chloride (1.85 mL, 21.23 mmol). The reaction mixture was allowed to stir at 0°C for 30 min and then allowed to warm to 25°C where it was stirred for 2 h. The reaction mixture was concentrated *in vacuo* to provide an orange semi-solid residue. This residue was

15 treated with a small amount of methylene chloride and was slowly added to a cooled (0°C) solution of 6-aminonicotinic acid methyl ester (776 mg, 5.10 mmol) and triethylamine (1.19 mL, 8.50 mmol) in methylene chloride (10 mL). The resulting reaction mixture was stirred at 0°C and allowed to warm to 25°C. The reaction mixture was stirred at 25°C for 15 h. The reaction mixture was then concentrated *in vacuo* to remove methylene chloride. The resulting residue was partitioned between water and ethyl acetate, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (1 x 100 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1 hexanes/ethyl acetate) afforded 6-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-nicotinic acid methyl ester (325 mg, 18%) as a white solid: mp 63-65°C; EI-HRMS m/e calcd for C₂₇H₂₈N₂O₃ (M⁺) 428.2099, found 428.2100.

Example 23

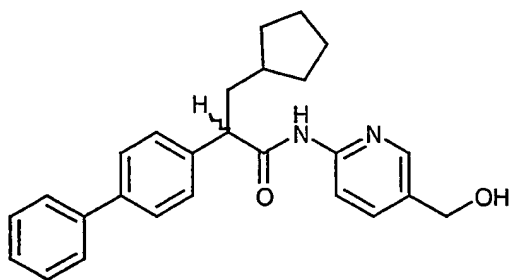
15 6-(2-Biphenyl-4-yl-3-cyclopentyl-propionylamino)-nicotinic acid



20 A solution of 6-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-nicotinic acid methyl ester (prepared in Example 22, 100 mg, 0.23 mmol) in methanol (2 mL) was treated with a 1N aqueous sodium hydroxide solution (350 mL, 0.35 mmol). The reaction mixture was heated under reflux for 30 min and then allowed to cool to 25°C. The reaction mixture was then concentrated *in vacuo*. The resulting residue was partitioned between water and ethyl acetate, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (1 x 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate then 100% methanol) afforded 6-

(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-nicotinic acid (27 mg, 28%) as a white solid: mp 271-272°C (dec); FAB-HRMS m/e calcd for $C_{26}H_{26}N_2O_3$ ($M+H$)⁺ 415.2021, found 415.2010.

5

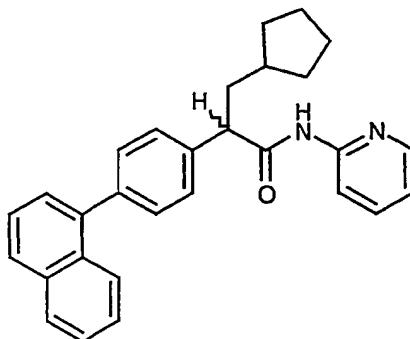
Example 24**2-Biphenyl-4-yl-3-cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-propionamide**

- 10 A solution of 6-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-nicotinic acid methyl ester (prepared in Example 22, 100 mg, 0.23 mmol) in diethyl ether (3 mL) at 0°C under nitrogen was slowly treated with lithium aluminum hydride powder (12 mg, 0.30 mmol). The resulting reaction mixture continued to stir at 0°C and was allowed to gradually warm to 25°C. The reaction mixture was then stirred at 25°C over a period of 64 h. The
- 15 reaction mixture was slowly quenched by the dropwise addition of water (5 mL). The resulting reaction mixture was partitioned between water and ethyl acetate, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (1 x 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/2
- 20 hexanes/ethyl acetate) afforded 2-biphenyl-4-yl-3-cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-propionamide (33 mg, 36%) as a white solid: mp 67-70°C; EI-HRMS m/e calcd for $C_{26}H_{28}N_2O_2$ (M^+) 400.2151, found 400.2147.

25

Example 25

(A) 3-Cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-N-pyridin-2-yl-propionamide



- 5 A solution of diisopropylamine (17.1 mL, 122.21 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (12.2 mL, 122.21 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and
- 10 then treated dropwise with a solution of 4-iodophenylacetic acid (15.25 g, 58.19 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (13.45 g, 64.02 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was
- 15 allowed to warm to 25°C where it was stirred for 42 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran and then quenched with a 10% aqueous hydrochloric acid solution (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and
- 20 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.97 g, 70%) as a cream solid: mp 121-122°C; EI-HRMS *m/e* calcd for C₁₄H₁₇IO₂ (M⁺) 344.0273, found 344.0275.
- 25 A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.00 g, 37.77 mmol) in methanol (94 mL) was treated slowly with concentrated sulfuric acid (5 drops). The

resulting reaction mixture was heated under reflux for 67 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (13.18 g, 97%) as a yellow semi-solid: EI-HRMS *m/e* calcd for C₁₅H₁₉IO₂ (M⁺) 358.0430, found 358.0434.

10 A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (3.87 g, 10.81 mmol), 1-naphthaleneboronic acid (2.79 g, 16.22 mmol), triethylamine (4.5 mL, 32.44 mmol), palladium (II) acetate (72.8 mg, 0.324 mmol), and tri-*o*-tolylphosphine (204.1 mg, 0.670 mmol) in dry *N,N*-dimethylformamide (43 mL) was heated at 100°C under nitrogen for 1 h. The reaction mixture was allowed to cool to 25°C and then concentrated
15 *in vacuo* to remove *N,N*-dimethylformamide. The residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL) and water (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic
20 acid methyl ester (3.51 g, 90%) as a yellow oil: EI-HRMS *m/e* calcd for C₂₅H₂₆O₂ (M⁺) 358.1933, found 358.1930.

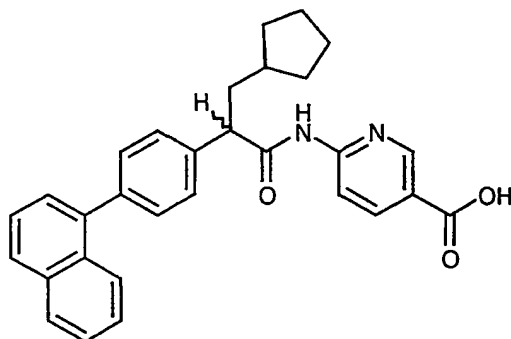
A solution of 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid methyl ester (3.32 g, 9.26 mmol) in tetrahydrofuran (12 mL) was treated with a 0.8M aqueous lithium
25 hydroxide solution (12 mL). The resulting reaction mixture was stirred at 25°C for 24 h, at which time, thin layer chromatography indicated the presence of starting material. The reaction mixture was then heated at 80°C for 18 h. The reaction mixture was then allowed to cool to 25°C and concentrated *in vacuo* to remove tetrahydrofuran. The residue was acidified to pH=2 with a 10% aqueous hydrochloric acid solution and then
30 extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck

Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid (1.74 g, 55%) as a white foam: mp 63-64°C; EI-HRMS m/e calcd for $C_{24}H_{24}O_2$ (M^+) 344.1776, found 344.1770.

- 5 A solution of 2-aminopyridine (25 mg, 0.26 mmol) in acetonitrile (500 μ L) was treated with 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid (75 mg, 0.22 mmol), triphenylphosphine (63 mg, 0.24 mmol), triethylamine (91 μ L, 0.66 mmol), and carbon tetrachloride (300 μ L). The resulting reaction mixture was stirred at 25°C for 15 h. The cloudy reaction mixture was diluted with water and then extracted with methylene
10 chloride. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded impure 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-N-pyridin-2-yl-propionamide. Repurification by flash chromatography (Merck Silica gel 60, 230-400 mesh, 100% methylene chloride) afforded pure 3-cyclopentyl-2-(4-naphthalen-1-yl-
15 phenyl)-N-pyridin-2-yl-propionamide. (40 mg, 43%) as a white foam: mp 73-77°C; EI-HRMS m/e calcd for $C_{29}H_{28}N_2O$ (M^+) 420.2202, found 420.2003.

(B) In an analogous manner, there was obtained:

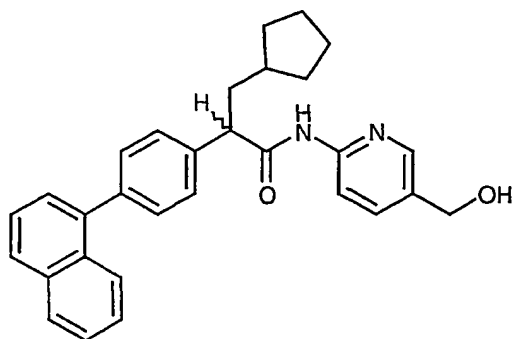
- (a) From 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid and 6-
20 aminonicotinic acid methyl ester: 6-[3-Cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-nicotinic acid methyl ester as a pale yellow foam: mp 78-82°C; EI-HRMS m/e calcd for $C_{31}H_{30}N_2O_3$ (M^+) 478.2256, found 478.2254.

Example 26**6-[3-Cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-nicotinic acid**

5

A solution of 6-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-nicotinic acid methyl ester (prepared in Example 25B-a, 45 mg, 0.094 mmol) in methanol (500 μ L) was treated with a 1N aqueous sodium hydroxide solution (188 μ L, 0.188 mmol). The reaction mixture was heated under reflux for 1 h and then allowed to cool to 25°C. The reaction mixture was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 15/1 methylene chloride/methanol) afforded 6-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-nicotinic acid (15 mg, 34%) as a pale yellow solid: mp 155-158°C; FAB-HRMS *m/e* calcd for $C_{30}H_{28}N_2O_3$ ($M+H$)⁺ 465.2178, found 465.2169.

15

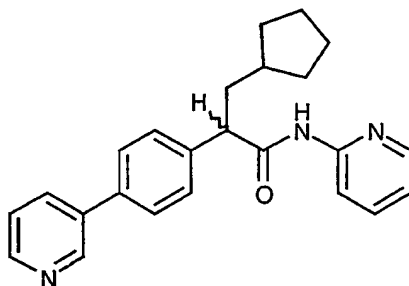
Example 27**3-Cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-2-(4-naphthalen-1-yl-phenyl)-propionamide**

20

A solution 6-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-nicotinic acid methyl ester (prepared in Example 25B-a, 140 mg, 0.29 mmol) in diethyl ether (2 mL) was cooled to 0°C and then slowly treated with lithium aluminum hydride powder (17 mg, 0.44 mmol). The reaction mixture was stirred at 0°C for 30 min and then allowed to warm to 25°C where it was stirred for 3.5 h. The reaction mixture was then slowly quenched by the dropwise addition of water (5 mL). The resulting mixture was partitioned between water (25 mL) and ethyl acetate (25 mL), and the layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-2-(4-naphthalen-1-yl-phenyl)-propionamide (47 mg, 37%) as a light yellow foam: mp 72-75°C; EI-HRMS *m/e* calcd for C₃₀H₃₀N₂O₂ (M⁺) 450.2307, found 450.2312.

Example 28

3-Cyclopentyl-N-pyridin-2-yl-2-(4-pyridin-3-yl-phenyl)-propionamide



A solution of diisopropylamine (17.1 mL, 122.21 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (12.2 mL, 122.21 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-iodophenylacetic acid (15.25 g, 58.19 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (13.45 g, 64.02 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was

allowed to warm to 25°C where it was stirred for 42 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran and then quenched with a 10% aqueous hydrochloric acid solution (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.97 g, 70%) as a cream solid: mp 121-122°C; EI-HRMS *m/e* calcd for C₁₄H₁₇IO₂ (M⁺) 344.0273, found 344.0275.

A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.00 g, 37.77 mmol) in methanol (94 mL) was treated slowly with concentrated sulfuric acid (5 drops). The resulting reaction mixture was heated under reflux for 67 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (13.18 g, 97%) as a yellow semi-solid: EI-HRMS *m/e* calcd for C₁₅H₁₉IO₂ (M⁺) 358.0430, found 358.0434.

A slurry of dichlorobis(triphenylphosphine)palladium(II) (119 mg, 0.17 mmol) in 1,2-dimethoxyethane (10 mL) was treated with 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (1.00 g, 2.79 mmol). The reaction slurry was stirred at 25°C for 10 min and then treated with a solution of pyridine-3-boronic acid (515 mg, 4.19 mmol) and a 2M aqueous sodium carbonate solution (2.8 mL, 5.58 mmol) in water (5 mL). The resulting reaction mixture was heated under reflux for 90 min. The reaction mixture was allowed to cool to 25°C and then filtered to remove the catalyst. The filtrate was partitioned between water and methylene chloride, and the layers were separated. The aqueous layer was further extracted with methylene chloride (75 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*.

Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionic acid methyl ester (800 mg, 92%) as a brown oil: EI-HRMS m/e calcd for $C_{20}H_{23}NO_2$ (M^+) 309.1729, found 309.1728.

5

A solution of 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionic acid methyl ester (450 mg, 1.45 mmol) in tetrahydrofuran (5 mL) was treated with a 0.8M aqueous lithium hydroxide solution (2.18 mL, 1.74 mmol). The resulting reaction mixture was stirred at 25°C for 3 d. The reaction mixture was then partitioned between water (50 mL) and ethyl acetate (50 mL), and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The resulting solid was purified by precipitation from methylene chloride/ethyl acetate to afford 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionic acid (271 mg, 63%) as a white solid: mp 136-138°C; EI-HRMS m/e calcd for $C_{19}H_{21}NO_2$ (M^+) 295.1572, found 295.1572.

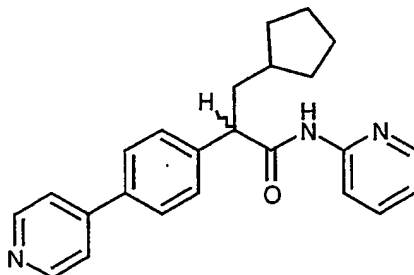
15

A solution of triphenylphosphine (133 mg, 0.51 mmol) in methylene chloride (5 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (90 mg, 0.51 mmol). The reaction mixture was stirred at 0°C for 20 min and then treated with 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionic acid (125 mg, 0.42 mmol). The resulting reaction mixture was stirred at 0°C for 5 min and then allowed to warm to 25°C where it was stirred for 20 min. The reaction mixture was then treated with 2-aminopyridine (88 mg, 0.93 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/2 hexanes/ethyl acetate) to afford impure 3-cyclopentyl-*N*-pyridin-2-yl-2-(4-pyridin-3-yl-phenyl)-propionamide as a pink foam. The impure foam was dissolved in methylene chloride (40 mL) and washed with a saturated aqueous sodium bicarbonate solution (1 x 40 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated *in vacuo* to afford pure 3-cyclopentyl-*N*-pyridin-2-yl-2-(4-pyridin-3-yl-phenyl)-propionamide (75 mg, 48%) as a pink foam: mp 139-140°C; EI-HRMS m/e calcd for $C_{24}H_{25}N_3O$ (M^+) 371.1998, found 371.2006.

25
30

Example 29

3-Cyclopentyl-N-pyridin-2-yl-2-(4-pyridin-4-yl-phenyl)-propionamide



5 A solution of diisopropylamine (17.1 mL, 122.21 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (12.2 mL, 122.21 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-iodophenylacetic acid (15.25 g, 58.19 mmol) in
 10 dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (13.45 g, 64.02 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 42 h. The reaction mixture was
 15 concentrated *in vacuo* to remove tetrahydrofuran and then quenched with a 10% aqueous hydrochloric acid solution (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1
 20 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.97 g, 70%) as a cream solid: mp 121-122°C; EI-HRMS *m/e* calcd for C₁₄H₁₇IO₂ (M⁺) 344.0273, found 344.0275.

A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.00 g, 37.77 mmol) in
 25 methanol (94 mL) was treated slowly with concentrated sulfuric acid (5 drops). The resulting reaction mixture was heated under reflux for 67 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue

was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (13.18 g, 97%) as a yellow semi-solid: EI-HRMS *m/e* calcd for C₁₅H₁₉IO₂ (M⁺) 358.0430, found 358.0434.

A slurry of dichlorobis(triphenylphosphine)palladium(II) (119 mg, 0.17 mmol) in 1,2-dimethoxyethane (10 mL) was treated with 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (1.00 g, 2.79 mmol). The reaction slurry was stirred at 25°C for 10 min and then treated with a solution of pyridine-4-boronic acid (515 mg, 4.19 mmol) and a 2M aqueous sodium carbonate solution (2.8 mL, 5.58 mmol) in water (5 mL). The resulting reaction mixture was heated under reflux for 8 h. The reaction mixture was allowed to cool to 25°C where it was stirred for 3 d. The reaction mixture was partitioned between water (75 mL) and methylene chloride (75 mL), and the layers were separated. The aqueous layer was further extracted with methylene chloride (75 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-propionic acid methyl ester (240 mg, 28%) as a brown oil that was used without further purification and characterization.

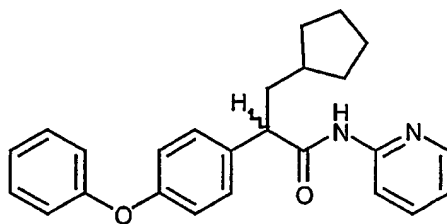
A solution of 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-propionic acid methyl ester (240 mg, 0.78 mmol) in tetrahydrofuran (3 mL) was treated with a 0.8M aqueous lithium hydroxide solution (1.45 mL, 1.16 mmol). The resulting reaction mixture was stirred at 25°C for 30 min and then heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C and then partitioned between water (100 mL) and ethyl acetate (70 mL). The layers were separated, and the aqueous layer was further extracted with ethyl acetate (1 x 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford a yellow oil that solidified upon sitting. The solid was collected to afford 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-propionic acid (127 mg,

55%) as a yellow solid: mp 118-121°C; FAB-HRMS m/e calcd for $C_{19}H_{21}NO_2$ ($M+H$)⁺ 296.1650, found 296.1658.

A solution of triphenylphosphine (59 mg, 0.22 mmol) in methylene chloride (1 mL) was cooled to 0°C and then slowly treated with *N*-bromosuccinimide (39 mg, 0.22 mmol). The reaction mixture was stirred at 0°C for 20 min and then treated with 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-propionic acid (55 mg, 0.19 mmol). The resulting reaction mixture was stirred at 0°C for 10 min and then allowed to warm to 25°C, where it was stirred for 20 min. The reaction mixture was then treated with 2-aminopyridine (39 mg, 0.41 mmol). The resulting reaction mixture was stirred at 25°C for 15 h. The crude reaction mixture was then directly purified by flash chromatography (Merck Silica gel 60, 230-400 mesh, 20/1 methylene chloride/methanol) to afford impure 3-cyclopentyl-*N*-pyridin-2-yl-2-(4-pyridin-4-yl-phenyl)-propionamide as a yellow solid. Repurification by flash chromatography (Merck Silica gel 60, 230-400 mesh, 100% ethyl acetate) afforded pure 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-*N*-thiazol-2-yl-propionamide (10 mg, 14%) as a yellow solid: mp 165-167°C; EI-HRMS m/e calcd for $C_{24}H_{25}N_3O$ (M^+) 371.1998, found 371.1998.

Example 30

(A) 3-Cyclopentyl-2-(4-phenoxy-phenyl)-*N*-pyridin-2-yl-propionamide



A solution of 3-cyclopentyl-2-(4-phenoxy-phenyl)-propionic acid (prepared in Example 12A, 51 mg, 0.16 mmol) in methylene chloride (10 mL) and one drop of *N,N*-dimethylformamide was cooled to 0°C and then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.10 mL, 0.18 mmol). The reaction mixture was stirred at 0°C for 30 min and then treated with a solution of 2-aminopyridine (32 mg, 0.34

mmol) in tetrahydrofuran (2 mL) and *N,N*-diisopropylethylamine (0.07 mL, 0.39 mmol). The reaction mixture was stirred at 25°C for 14 h. At this time, the reaction mixture was diluted with water (10 mL) and then extracted with methylene chloride (3 x 10 mL). The combined organic extracts were washed with water (1 x 10 mL), a 1N aqueous sodium hydroxide solution (1 x 10 mL), and a 1N aqueous hydrochloric acid solution (1 x 10 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 90/10 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-phenoxy-phenyl)-N-pyridin-2-yl-propionamide (22 mg, 35%) as glassy solid: EI-HRMS *m/e* calcd for C₂₅H₂₆N₂O₂ (M⁺) 386.1994, found 386.2001.

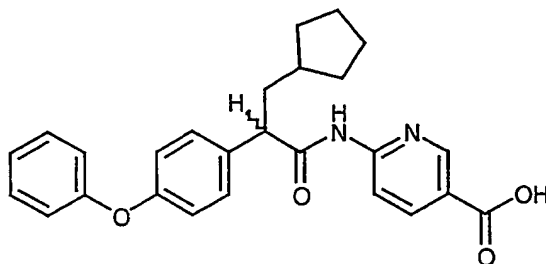
(B) In an analogous manner, there were obtained:

(a) From 3-cyclopentyl-2-(4-phenoxy-phenyl)propionic acid and 2-amino-5-methylpyridine: 3-Cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-phenoxy-phenyl)-propionamide as a glassy solid: FAB-HRMS *m/e* calcd for C₂₆H₂₈N₂O₂ (M+H)⁺ 401.2229, found 401.2229.

(b) From 3-cyclopentyl-2-(4-phenoxy-phenyl)propionic acid and 2-amino-nicotinic acid methyl ester: 6-[3-Cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-nicotinic acid methyl ester as a white foam: FAB-HRMS *m/e* calcd for C₂₇H₂₈N₂O₄ (M+H)⁺ 445.2127, found 445.2127.

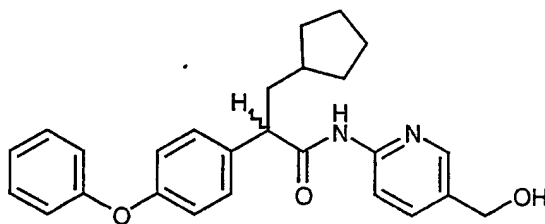
Example 31

6-[3-Cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-nicotinic acid



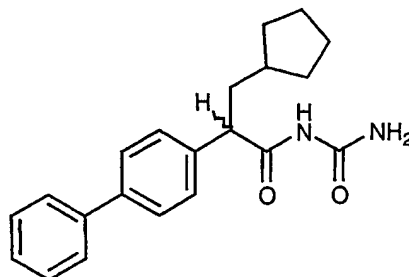
A solution of 6-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-nicotinic acid methyl ester (prepared in Example 30B-b, 102 mg, 0.23 mmol) in ethanol (10 mL) at 25°C was treated with a solution of potassium hydroxide (40 mg, 0.69 mmol) in water (2.5 mL). This light yellow solution was stirred at 25°C for 2 h and then concentrated *in vacuo* to remove ethanol. The resulting aqueous solution was acidified to pH=2 with a 1N aqueous hydrochloric acid solution and then extracted with methylene chloride (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 10/90 hexanes/ethyl acetate plus 1% acetic acid) afforded 6-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-nicotinic acid (74 mg, 76%) as a white solid: FAB-HRMS *m/e* calcd for C₂₆H₂₆N₂O₄ (M+H)⁺ 431.1971, found 431.1987.

Example 32
3-Cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-2-(4-phenoxy-phenyl)-propionamide



A solution of 6-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-nicotinic acid methyl ester (prepared in Example 30B-b, 59 mg, 0.13 mmol) in diethyl ether (5 mL) was cooled to 0°C and then treated with lithium aluminum hydride (8 mg, 0.20 mmol). The reaction was slowly warmed to 25°C where it was stirred for 16 h. At this time, the reaction mixture was slowly diluted with water (5 mL) and then extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-2-(4-phenoxy-phenyl)-propionamide (28 mg, 51%) as a yellow foam: FAB-HRMS *m/e* calcd for C₂₆H₂₈N₂O₃ (M+H)⁺ 417.2178, found 417.2163.

Example 33
(2-Biphenyl-4-yl-3-cyclopentyl-propionyl) urea



5 A solution of diisopropylamine (6.93 mL, 49.5 mmol) in dry tetrahydrofuran (64 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (16 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (19.8 mL, 49.5 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then
10 treated dropwise with a solution of 4-biphenylacetic acid (5.00 g, 23.6 mmol) in a small amount of dry tetrahydrofuran. The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (4.96 g, 23.6 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C over a period of 15 h. The reaction
15 mixture was quenched with water (100 mL), and the reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous layer was acidified to pH=2 with concentrated hydrochloric acid and then extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1
20 hexanes/ethyl acetate) afforded 2-biphenyl-4-yl-3-cyclopentylpropionic acid (5.13 g, 74%) as a white solid: mp 131-133°C; FAB-HRMS *m/e* calcd for C₂₀H₂₂O₂ (M+H)⁺ 294.1620, found 294.1626.

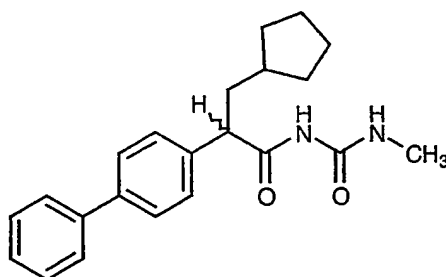
A solution of 2-biphenyl-4-yl-3-cyclopentylpropionic acid (192.3 mg, 0.653 mmol) in
25 methanol (3.3 mL) was treated slowly with concentrated sulfuric acid (1 drop). The resulting reaction mixture was heated under reflux for 24 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue

was diluted with ethyl acetate (50 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL), water (1 x 100 mL), and a saturated aqueous sodium chloride solution (1 x 100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 9/1 hexanes/ethyl acetate) afforded 2-biphenyl-4-yl-3-cyclopentylpropionic acid methyl ester (191.5 mg, 95%) as a yellow oil: EI-HRMS *m/e* calcd for $C_{21}H_{24}O_2$ (M^+) 308.1776, found 308.1774.

A mixture of 2-biphenyl-4-yl-3-cyclopentylpropionic acid methyl ester (415.5 mg, 1.35 mmol) and urea (202.3 mg, 3.37 mmol, 2.5 equiv) was treated with a solution of magnesium methoxide in methanol (7.4 wt.%, 7.7 mL, 5.39 mmol). The resulting reaction mixture was then heated under reflux for 23 h. The reaction mixture was allowed to cool to 25°C and then filtered through celite. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate then 1/1 hexanes/ethyl acetate) afforded (2-biphenyl-4-yl-3-cyclopentylpropionyl) urea (67.8 mg, 15%) as a white solid: mp 184-185°C; FAB-HRMS *m/e* calcd for $C_{21}H_{24}N_2O_2$ ($M+H$)⁺ 337.1917, found 337.1924.

Example 34

1-(2-Biphenyl-4-yl-3-cyclopentyl-propionyl)-3-methyl urea



A solution of diisopropylamine (6.93 mL, 49.5 mmol) in dry tetrahydrofuran (64 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (16 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (19.8 mL, 49.5 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then

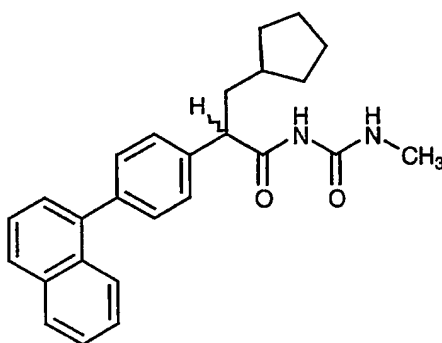
treated dropwise with a solution of 4-biphenylacetic acid (5.00 g, 23.6 mmol) in a small amount of dry tetrahydrofuran. The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (4.96 g, 23.6 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C over a period of 15 h. The reaction mixture was quenched with water (100 mL), and the reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran. The remaining aqueous layer was acidified to pH=2 with concentrated hydrochloric acid and then extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 2/1 hexanes/ethyl acetate) afforded 2-biphenyl-4-yl-3-cyclopentylpropionic acid (5.13 g, 74%) as a white solid: mp 131-133°C; FAB-HRMS m/e calcd for C₂₀H₂₂O₂ (M+H)⁺ 294.1620, found 294.1626.

A solution of 2-biphenyl-4-yl-3-cyclopentylpropionic acid (192.3 mg, 0.653 mmol) in methanol (3.3 mL) was treated slowly with concentrated sulfuric acid (1 drop). The resulting reaction mixture was heated under reflux for 24 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (50 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL), water (1 x 100 mL), and a saturated aqueous sodium chloride solution (1 x 100 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 9/1 hexanes/ethyl acetate) afforded 2-biphenyl-4-yl-3-cyclopentylpropionic acid methyl ester (191.5 mg, 95%) as a yellow oil: EI-HRMS m/e calcd for C₂₁H₂₄O₂ (M⁺) 308.1776, found 308.1774.

A mixture of 2-biphenyl-4-yl-3-cyclopentylpropionic acid methyl ester (987.4 mg, 3.20 mmol) and methyl urea (948.7 mg, 12.80 mmol) was treated with a solution of magnesium methoxide in methanol (7.4 wt.%, 18 mL, 12.80 mmol). The resulting reaction mixture was then heated under reflux for 19 h. The reaction mixture was allowed to cool to 25°C and then filtered through celite. The filtrate was concentrated *in*

vacuo. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 1-(2-biphenyl-4-yl-3-cyclopentyl-propionyl)-3-methyl urea (152.5 mg, 14%) as a white solid: mp 195-197°C; EI-HRMS *m/e* calcd for C₂₂H₂₆N₂O₂ (M⁺) 350.1994, found 350.2004.

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Example 35**1-[3-Cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionyl]-3-methyl urea**

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A solution of diisopropylamine (17.1 mL, 122.21 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (12.2 mL, 122.21 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-iodophenylacetic acid (15.25 g, 58.19 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (13.45 g, 64.02 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 42 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran and then quenched with a 10% aqueous hydrochloric acid solution (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.97 g,

25

70%) as a cream solid: mp 121-122°C; EI-HRMS m/e calcd for $C_{14}H_{17}IO_2$ (M^+) 344.0273, found 344.0275.

5 A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.00 g, 37.77 mmol) in methanol (94 mL) was treated slowly with concentrated sulfuric acid (5 drops). The resulting reaction mixture was heated under reflux for 67 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and
10 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (13.18 g, 97%) as a yellow semi-solid: EI-HRMS m/e calcd for $C_{15}H_{19}IO_2$ (M^+) 358.0430, found 358.0434.

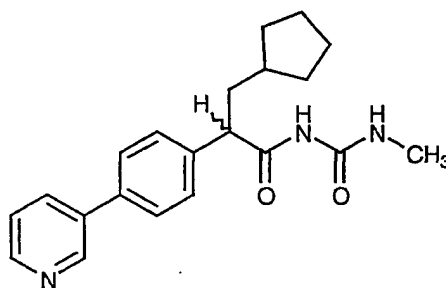
15 A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (3.87 g, 10.81 mmol), 1-naphthaleneboronic acid (2.79 g, 16.22 mmol), triethylamine (4.5 mL, 32.44 mmol), palladium (II) acetate (72.8 mg, 0.324 mmol), and tri-*o*-tolylphosphine (204.1 mg, 0.670 mmol) in dry N,N-dimethylformamide (43 mL) was heated at 100°C under nitrogen for 1 h. The reaction mixture was allowed to cool to 25°C and then concentrated
20 *in vacuo* to remove N,N-dimethylformamide. The residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium bicarbonate solution (1 x 100 mL) and water (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic
25 acid methyl ester (3.51 g, 90%) as a yellow oil: EI-HRMS m/e calcd for $C_{25}H_{26}O_2$ (M^+) 358.1933, found 358.1930.

A mixture of 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionic acid methyl ester (196.5 mg, 0.548 mmol) and methyl urea (121.8 mg, 1.64 mmol) was treated with a
30 solution of magnesium methoxide in methanol (7.4 wt.%, 3.1 mL, 2.19 mmol). The resulting reaction mixture was then heated under reflux for 24 h. The reaction mixture

was allowed to cool to 25°C and then filtered through celite. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 9/1 hexanes/ethyl acetate then 3/1 to 1/1 hexanes/ethyl acetate gradient elution) afforded 1-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionyl]-3-methyl urea (76.9 mg, 35%) as a white foam: mp 85-88°C; EI-HRMS *m/e* calcd for C₂₆H₂₈N₂O₂ (M⁺) 400.2151, found 400.2150.

Example 36

1-[3-Cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionyl]-3-methyl-urea



A solution of diisopropylamine (17.1 mL, 122.21 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (12.2 mL, 122.21 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-iodophenylacetic acid (15.25 g, 58.19 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (13.45 g, 64.02 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was allowed to warm to 25°C where it was stirred for 42 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran and then quenched with a 10% aqueous hydrochloric acid solution (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1

hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.97 g, 70%) as a cream solid: mp 121-122°C; EI-HRMS m/e calcd for $C_{14}H_{17}IO_2$ (M^+) 344.0273, found 344.0275.

- 5 A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.00 g, 37.77 mmol) in methanol (94 mL) was treated slowly with concentrated sulfuric acid (5 drops). The resulting reaction mixture was heated under reflux for 67 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and
10 concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (13.18 g, 97%) as a yellow semi-solid: EI-HRMS m/e calcd for $C_{15}H_{19}IO_2$ (M^+) 358.0430, found 358.0434.

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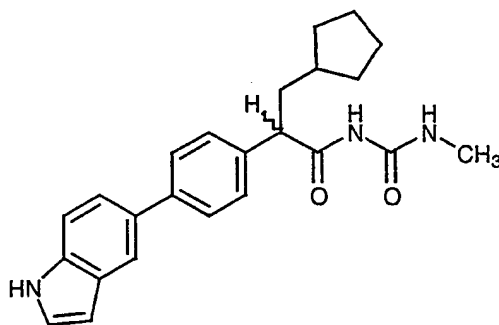
- A slurry of dichlorobis(triphenylphosphine)palladium(II) (119 mg, 0.17 mmol) in 1,2-dimethoxyethane (10 mL) was treated with 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (1.00 g, 2.79 mmol). The reaction slurry was stirred at 25°C for 10 min and then treated with a solution of pyridine-3-boronic acid (515 mg, 4.19 mmol) and a
20 2M aqueous sodium carbonate solution (2.8 mL, 5.58 mmol) in water (5 mL). The resulting reaction mixture was heated under reflux for 90 min. The reaction mixture was allowed to cool to 25°C and then filtered to remove the catalyst. The filtrate was partitioned between water and methylene chloride, and the layers were separated. The aqueous layer was further extracted with methylene chloride (75 mL). The combined
25 organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionic acid methyl ester (800 mg, 92%) as a brown oil: EI-HRMS m/e calcd for $C_{20}H_{23}NO_2$ (M^+) 309.1729, found 309.1728.

30

A mixture of 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionic acid methyl ester (275 mg, 0.89 mmol) and methyl urea (165 mg, 2.22 mmol) was treated with a solution of magnesium methoxide in methanol (7.4 wt.%, 5.5 mL, 2.67 mmol). The reaction mixture was then concentrated *in vacuo* to approximately one-half the volume of methanol. The resulting reaction mixture was then heated under reflux for 3 d. The reaction mixture was allowed to cool to 25°C and then partitioned between water and ethyl acetate. The layers were separated, and the aqueous layer was further extracted with ethyl acetate (2 x 40 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/3 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionyl]-3-methyl-urea (17 mg, 6%) as a white solid: mp 158-160°C; FAB-HRMS *m/e* calcd for C₂₁H₂₅N₃O₂ (M+H)⁺ 352.2025, found 352.2028.

Example 37

15 1-{3-Cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-propionyl}-3-methyl-urea



A solution of diisopropylamine (17.1 mL, 122.21 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL) was cooled to -78°C under nitrogen and then treated with a 10M solution of *n*-butyllithium in hexanes (12.2 mL, 122.21 mmol). The yellow reaction mixture was stirred at -78°C for 30 min and then treated dropwise with a solution of 4-iodophenylacetic acid (15.25 g, 58.19 mmol) in dry tetrahydrofuran (55 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (18 mL). The reaction mixture turned dark in color and was allowed to stir at -78°C for 45 min, at which time, a solution of iodomethylcyclopentane (13.45 g, 64.02 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was

allowed to warm to 25°C where it was stirred for 42 h. The reaction mixture was concentrated *in vacuo* to remove tetrahydrofuran and then quenched with a 10% aqueous hydrochloric acid solution (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.97 g, 70%) as a cream solid: mp 121-122°C; EI-HRMS *m/e* calcd for C₁₄H₁₇IO₂ (M⁺) 344.0273, found 344.0275.

10

A solution of 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid (13.00 g, 37.77 mmol) in methanol (94 mL) was treated slowly with concentrated sulfuric acid (5 drops). The resulting reaction mixture was heated under reflux for 67 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with ethyl acetate (300 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 100% hexanes then 19/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (13.18 g, 97%) as a yellow semi-solid: EI-HRMS *m/e* calcd for C₁₅H₁₉IO₂ (M⁺) 358.0430, found 358.0434.

20

A slurry of dichlorobis(triphenylphosphine)palladium(II) (119 mg, 0.17 mmol) in 1,2-dimethoxyethane (10 mL) was treated with 3-cyclopentyl-2-(4-iodo-phenyl)-propionic acid methyl ester (1.00 g, 2.79 mmol). The reaction slurry was stirred at 25°C for 10 min and then treated with a mixture of 5-indolylboronic acid (670 mg, 4.19 mmol) in water (5 mL) and a 2M aqueous sodium carbonate solution (2.8 mL, 5.58 mmol). The resulting reaction mixture was heated under reflux for 2 h. The reaction mixture was allowed to cool to 25°C and then filtered to remove the catalyst. The filtrate was partitioned between water (50 mL) and methylene chloride (50 mL), and the layers were separated. The aqueous layer was further extracted with methylene chloride (50 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated

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in vacuo. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 1/2 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-propionic acid methyl ester (347 mg, 36%) as a light brown oil: EI-HRMS *m/e* calcd for $C_{23}H_{25}NO_2$ (M^+) 347.1885, found 347.1887.

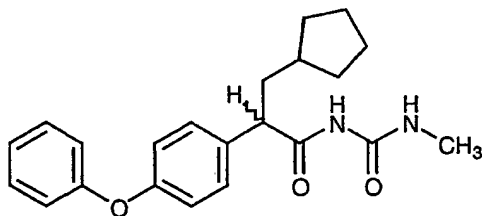
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A mixture of 3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-propionic acid methyl ester (245 mg, 0.71 mmol) and methyl urea (131 mg, 1.76 mmol) was treated with a solution of magnesium methoxide in methanol (7.4 wt.%, 5.5 mL, 2.12 mmol). The reaction mixture was then concentrated *in vacuo* to approximately one-half the volume of methanol. The resulting reaction mixture was then heated under reflux for 15 h. The reaction mixture was allowed to cool to 25°C and then partitioned between water (20 mL) and ethyl acetate (50 mL). The layers were separated, and the aqueous layer was further extracted with ethyl acetate (1 x 25 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck
15 Silica gel 60, 230-400 mesh, 1/1 hexanes/ethyl acetate) afforded 1-{3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-propionyl}-3-methyl-urea (79 mg, 29%) as a white foam: mp 91-95°C (foam to gel); FAB-HRMS *m/e* calcd for $C_{24}H_{27}N_3O_2$ ($M+H$)⁺ 390.2181, found 390.2192.

20

Example 38

1-[3-Cyclopentyl-2-(4-phenoxy-phenyl)-propionyl]-3-methyl-urea



25 A solution of diisopropylamine (2.52 mL, 19.3 mmol) in tetrahydrofuran (50 mL) was cooled to -78°C under a nitrogen atmosphere and then treated with a 2.5M solution of *n*-butyllithium in hexanes (7.7 mL, 19.3 mmol). The reaction mixture was stirred at -78°C for 15 min and then slowly treated with a solution of 4-phenoxyphenylacetic acid (2.00 g, 8.8 mmol) in tetrahydrofuran (12 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-

pyrimidinone (4 mL) via cannulation. The resulting bright yellow solution was allowed to stir for 1 h at -78°C. After this time, the reaction mixture was treated with a solution of iodomethylcyclopentane (2.02 g, 9.6 mmol) in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1 mL) via cannulation. The resulting reaction mixture was stirred for 1 h
5 at -78°C and then allowed to warm to 25°C where it was stirred for 14 h. The reaction was then acidified to pH=2 by the dropwise addition of a 1N aqueous hydrochloric acid solution and then extracted with ethyl acetate (3 x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate plus
10 1% acetic acid) afforded 3-cyclopentyl-2-(4-phenoxy-phenyl)propionic acid (2.49 g, 91%) as a white foam: EI-HRMS m/e calcd for C₂₀H₂₂O₃ (M⁺) 310.1568, found 310.1568.

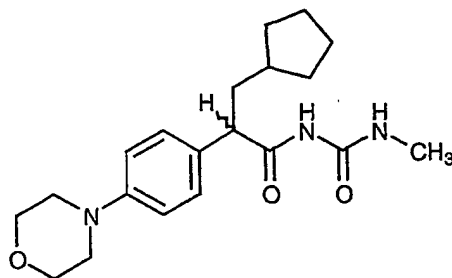
A solution of 3-cyclopentyl-2-(4-phenoxy-phenyl)-propionic acid (200 mg, 0.64 mmol) in
15 methylene chloride (10 mL) with one drop of *N,N*-dimethylformamide was cooled to 0°C under a nitrogen atmosphere. The reaction mixture was then treated with a 2.0M solution of oxalyl chloride in methylene chloride (0.48 mL, 0.97 mmol), and the resulting reaction mixture was stirred at 0°C for 30 min. The reaction mixture was then treated with
20 1,1,1,3,3,3-hexamethyldisilazane (0.47 mL, 2.24 mmol) and then allowed to warm to 25°C where it was stirred for 16 h. After such time, the reaction mixture was treated with methanol (10 mL) and then allowed to stir at 25°C for 10 min. The resulting reaction mixture was washed with a 5% aqueous sulfuric acid solution (2 x 10 mL). The combined aqueous extracts were further extracted with methylene chloride (2 x 10 mL). The combined organic extracts were then washed with a saturated aqueous sodium
25 chloride solution (1 x 10 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-phenoxy-phenyl)-propionamide (120 mg, 61%,) as a white solid: mp 91.6-94.4°C; EI-HRMS m/e calcd for C₂₀H₂₃NO₂ (M⁺) 309.1729, found 309.1733.

30

A solution of 3-cyclopentyl-2-(4-phenoxy-phenyl)-propionamide (143 mg, 0.46 mmol) in toluene (10 mL) was treated with methyl isocyanate (0.04 mL, 0.69 mmol). The reaction mixture was heated under reflux for 24 h. The reaction was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionyl]-3-methyl-urea (116 mg, 69%) as a white solid: EI-HRMS *m/e* calcd for C₂₂H₂₆N₂O₃ (M⁺) 366.1943, found 366.1946.

Example 39

10 1-[3-Cyclopentyl-2-(4-morpholin-4-yl-phenyl)-propionyl]-3-methyl-urea



A mixture of 4-morpholinoacetophenone (4.61 g, 22 mmol), sulfur (2.16 g, 67 mmol), and morpholine (6 mL, 67 mmol) was heated at 80°C for 1h then heated under reflux for 15 18 h. The hot reaction mixture was poured into warm ethanol. Upon cooling to 25°C, a precipitate formed. The precipitate was filtered to provide a tan solid (4.16 g). This crude tan solid was then treated with concentrated acetic acid (16 mL), concentrated sulfuric acid (2.4 mL), and water (3.6 mL). The resulting reaction mixture was heated under reflux for 4 h and then poured into water. The water was removed *in vacuo* to provide crude (4-morpholin-4-yl-phenyl)-acetic acid as a brown oil (8.20 g). This crude (4-morpholin-4-yl-phenyl)-acetic acid was dissolved in methanol (100 mL) and then slowly treated with concentrated sulfuric acid (1 mL). The reaction mixture was heated under reflux for 66 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with water (200 mL) 20 to provide crude (4-morpholin-4-yl-phenyl)-acetic acid as a brown oil (8.20 g). This crude (4-morpholin-4-yl-phenyl)-acetic acid was dissolved in methanol (100 mL) and then slowly treated with concentrated sulfuric acid (1 mL). The reaction mixture was heated under reflux for 66 h. The reaction mixture was allowed to cool to 25°C and then concentrated *in vacuo* to remove methanol. The residue was diluted with water (200 mL) 25 and then treated with a 10% aqueous sodium hydroxide solution until pH=9. The aqueous phase was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed with a saturated aqueous sodium chloride solution (1 x 100 mL),

dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 70-230 mesh, 3/1 to 1/1 hexanes/ethyl acetate gradient elution) afforded (4-morpholin-4-yl-phenyl)-acetic acid methyl ester (2.22 g, 42% for 3 steps) as a yellow oil: EI-HRMS *m/e* calcd for $C_{13}H_{17}NO_3$ (M^+) 235.1208, found 235.1214.

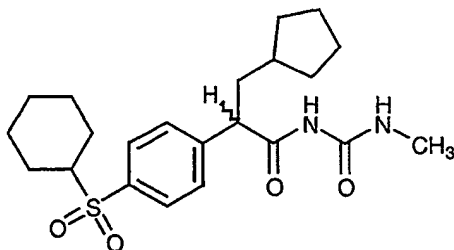
5

A solution of diisopropylamine (344 μ L, 2.45 mmol) in dry tetrahydrofuran (2.9 mL) was cooled to -78°C under nitrogen and then treated with a 2.5M solution of *n*-butyllithium in hexanes (981 μ L, 2.45 mmol). The reaction mixture was stirred at -78°C for 15 min and then treated dropwise with a solution of (4-morpholin-4-yl-phenyl)-acetic acid methyl ester (549.9 mg, 2.34 mmol) in dry tetrahydrofuran (2 mL) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (1 mL). The resulting reaction mixture was allowed to stir at -78°C for 30 min, at which time, a solution of iodomethylcyclopentane (540.0 mg, 2.57 mmol) in a small amount of dry tetrahydrofuran was added dropwise. The reaction mixture was then allowed to warm to 25°C where it was stirred for 67 h. The reaction mixture was quenched with water and then concentrated *in vacuo* to remove tetrahydrofuran. The aqueous residue was diluted with ethyl acetate (200 mL). The organic phase was washed with a saturated aqueous sodium chloride solution (1 x 100 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-propionic acid methyl ester (381.4 mg, 51%) as a white solid: mp $68-70^\circ\text{C}$; EI-HRMS *m/e* calcd for $C_{19}H_{27}NO_3$ (M^+) 317.1991, found 317.2001.

A mixture of 3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-propionic acid methyl ester (364.0 mg, 1.15 mmol) and methyl urea (254.8 mg, 3.44 mmol) was treated with a solution of magnesium methoxide in methanol (7.4 wt.%, 6.6 mL, 4.59 mmol). The resulting reaction mixture was heated under reflux for 3 d. The reaction mixture was allowed to cool to 25°C and then filtered through a pad of celite. The pad of celite was washed well with ethyl acetate until the washings showed the absence of product by thin layer chromatography. The filtrate was then concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 3/1 hexanes/ethyl acetate then 1/1

hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-propionyl]-3-methyl-urea (43.5 mg, 11%) as a white solid: mp 206-207°C; FAB-HRMS m/e calcd for $C_{20}H_{29}N_3O_3$ (M^+) 359.2209, found 359.2206.

5

Example 40**1-[2-(4-Cyclohexanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea**

10

A solution of freshly prepared lithium diisopropylamide (430.55 mL of a 0.3M stock solution, 129.16 mmol) was cooled to -78°C and then treated with a solution of (4-nitro-phenyl)-acetic acid ethyl ester (26.32 g, 125.83 mmol) in tetrahydrofuran/hexamethylphosphoramide (312.5 mL, 3:1). The resulting solution was stirred at -78°C for 45 min. At this time, the reaction was treated with a solution of iodomethylcyclopentane (27.75 g, 132.1 mmol) in hexamethylphosphoramide (27.75 mL). The mixture was stirred at -78°C for 4 h. The reaction was then warmed to 25°C and was stirred at 25°C for 16 h. The reaction mixture was then quenched by the dropwise addition of a saturated aqueous ammonium chloride solution (250 mL). This mixture was concentrated *in vacuo*, diluted with water (250 mL), and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were washed with a saturated aqueous lithium chloride solution (2 x 250 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 98/2 hexanes/ethyl acetate) afforded 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (28.30 g, 77.2%) as a yellow oil: EI-HRMS m/e calcd for $C_{16}H_{21}NO_4$ (M^+) 291.1470, found 291.1470.

20

25

A solution of 3-cyclopentyl-2-(4-nitro-phenyl)-propionic acid ethyl ester (7.37 g, 25.3 mmol) in ethyl acetate (316 mL) was treated with 10% palladium on activated carbon (500 g). The reaction mixture was shaken under 60 psi of hydrogen gas at 25°C for 18 h. The catalyst was then filtered off through a pad of celite and was washed with ethyl acetate. The filtrate was concentrated *in vacuo* to give 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (3.52 g, 53.3%) as a yellow oil: EI-HRMS m/e calcd for C₁₆H₂₃NO₂ (M⁺) 261.1727, found 261.1727.

A mixture of concentrated hydrochloric acid (0.32 mL) and ice (320 mg) was cooled to 0°C and then treated with 2-(4-amino-phenyl)-3-cyclopentyl-propionic acid ethyl ester (419.4 mg, 1.60 mmol). After 5 min, a solution of sodium nitrite (117 mg, 1.70 mmol) in water (0.26 mL) was added to the reaction mixture. The resulting solution was stirred at 0°C for 5 min. At this time, the solution was added to a solution of cyclohexanethiol (0.23 mL, 1.86 mmol) in water (0.35 mL) warmed to 45°C. The reaction was stirred at 45°C for 12 h. At this time, the reaction was diluted with water (100 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was passed through a plug of silica (90/10 hexanes/ethyl acetate) to afford a crude brown oil (128.2 mg). This oil was dissolved in methylene chloride (8.8 mL), cooled to 0°C, and then treated with 3-chloroperoxybenzoic acid (80-85% grade, 307 mg, 1.77 mmol). The reaction mixture was stirred at 25°C for 1.5 h. At this time, the reaction was diluted with ethyl acetate (50 mL). This solution was washed with a saturated aqueous sodium bisulfite solution (1 x 50 mL) and a saturated aqueous sodium chloride solution (1 x 50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 80/20 hexanes/ethyl acetate) afforded 2-(4-cyclohexanesulfonyl-phenyl)-3-cyclopentyl-propionic acid ethyl ester (37.7 mg, 23.7%) as a brown oil: EI-HRMS m/e calcd for C₂₂H₃₂O₄S (M⁺) 392.2021 found 392.2022.

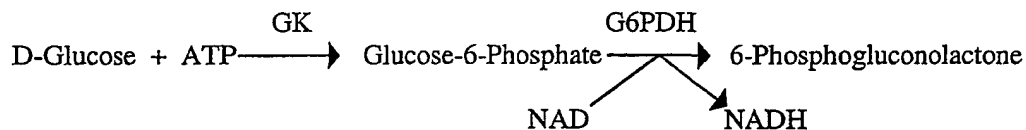
A mixture of 2-(4-cyclohexanesulfonyl-phenyl)-3-cyclopentyl-propionic acid ethyl ester (71.5 mg, 0.16 mmol) and methyl urea (18 mg, 0.24 mmol) was treated with a solution of

magnesium methoxide in methanol (7.4 wt.%, 0.46 mL, 0.32 mmol). The resulting reaction mixture was heated at 100°C for 8 h. At this time, the reaction was cooled to 25°C and passed through a plug of celite. The celite was washed with ethyl acetate. The filtrate was concentrated *in vacuo*. Flash chromatography (Merck Silica gel 60, 230-400 mesh, 50/50 hexanes/ethyl acetate) afforded 1-[3-cyclopentyl-2-(3,4-difluoro-phenyl)-propionyl]-3-methyl-urea (12.6mg, 18.7%) as a white solid: mp 244-246°C; FAB-HRMS m/e calcd for C₁₆H₂₀F₂N₂O₂ (M+H)⁺ 421.2153, found 421.2161.

Biological Activity Examples

Example A: *In Vitro* Glucokinase Activity

Glucokinase Assay: Glucokinase (GK) was assayed by coupling the production of glucose-6-phosphate to the generation of NADH with glucose-6-phosphate dehydrogenase (G6PDH, 0.75-1 kunits/mg; Boehringer Mannheim, Indianapolis, IN) from *Leuconostoc mesenteroides* as the coupling enzyme (Scheme 2). Recombinant



Scheme 2

Human liver GK1 was expressed in *E. coli* as a glutathione S-transferase fusion protein (GST-GK) [Liang et al, 1995] and was purified by chromatography over a glutathione-Sepharose 4B affinity column using the procedure provided by the manufacturer (Amersham Pharmacia Biotech, Piscataway, NJ). Previous studies have demonstrated that the enzymatic properties of native GK and GST-GK are essentially identical (Liang et al, 1995; Neet et al., 1990).

The assay was conducted at 25° C in a flat bottom 96-well tissue culture plate from Costar (Cambridge, MA) with a final incubation volume of 120 µl. The incubation

mixture contained: 25 mM Hepes buffer (pH, 7.1), 25 mM KCl, 5 mM D-glucose, 1mM ATP, 1.8 mM NAD, 2 mM MgCl₂, 1 μ M sorbitol-6-phosphate, 1 mM dithiothreitol, test drug or 10% DMSO, 1.8 unit/ml G6PDH, and GK (see below). All organic reagents were >98 % pure and were from Boehringer Mannheim with the exceptions of D-glucose
5 and Hepes that were from Sigma Chemical Co, St Louis, MO. Test compounds were dissolved in DMSO and were added to the incubation mixture minus GST-GK in a volume of 12 μ l to yield a final DMSO concentration of 10%. This mix was preincubated in the temperature controlled chamber of a SPECTRAMax 250 microplate spectrophotometer (Molecular Devices Corporation, Sunnyvale, CA) for 10 minutes to
10 allow temperature equilibrium and then the reaction was started by the addition of 20 μ l GST-GK.

After addition of enzyme, the increase in optical density (OD) at 340 nm was monitored over a 10 minute incubation period as a measure of GK activity. Sufficient
15 GST-GK was added to produce an increase in OD₃₄₀ of 0.08 to 0.1 units over the 10 minute incubation period in wells containing 10% DMSO, but no test compound. Preliminary experiments established that the GK reaction was linear over this period of time even in the presence of activators that produced a 5-fold increase in GK activity. The GK activity in control wells was compared with the activity in wells containing test
20 GK activators, and the concentration of activator that produced a 50% increase in the activity of GK, i.e., the SC_{1.5}, was calculated. All of the compounds of formula I described in the Synthesis Examples had an SC_{1.5} less than or equal to 30 μ M.

Example A

Tablets containing the following ingredients can be produced in a conventional manner:

5	<u>Ingredients</u>	<u>mg per tablet</u>
	Compound of formula (I)	10.0 - 100.0
	Lactose	125.0
	Corn starch	75.0
	Talc	4.0
10	Magnesium stearate	1.0

Example B

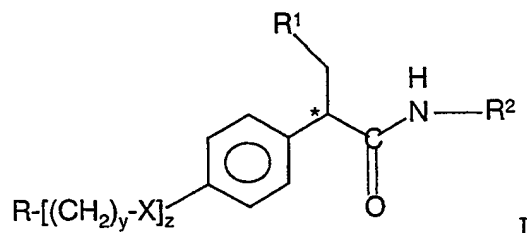
15 Capsules containing the following ingredients can be produced in a conventional manner:

	<u>Ingredients</u>	<u>mg per capsule</u>
	Compound of formula (I)	25.0
	Lactose	150.0
	Corn starch	20.0
20	Talc	5.0

Claims

1. An amide selected from the group consisting of a compound of the formula

5

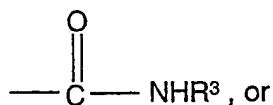


wherein

X is -O- or -S(O)₂-;

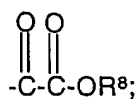
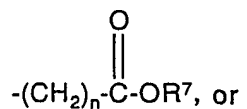
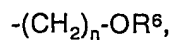
R is a heteroaromatic ring, connected by a ring carbon atom, which contains
 10 from 5 to 6 ring members with from 1 to 2 heteroatoms selected from the group
 consisting of oxygen, sulfur or nitrogen, aryl containing 6 or 10 ring carbon atoms, aryl
 containing from 6 to 10 ring carbon atoms fused with a heteroaromatic ring containing 5
 or 6 ring members with 1 or 2 heteroatoms in the ring being selected from the group
 consisting of nitrogen, oxygen or sulfur, or a saturated 5- or 6-membered
 15 cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group
 consisting of oxygen, sulfur and nitrogen, or a cycloalkyl ring having 5 or 6 carbon
 atoms; R¹ is a cycloalkyl ring having 5 or 6 carbon atoms;

R² is



20 a five- or six-membered heteroaromatic ring connected by a ring carbon atom to the
 amide group shown, which heteroaromatic ring contains from 1 to 3 heteroatoms selected
 from the group consisting of oxygen, sulfur and nitrogen with a first heteroatom being
 nitrogen which is adjacent to the connecting ring carbon atom, said heteroaromatic ring
 being unsubstituted or monosubstituted at a position on a ring carbon atom other than

adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl,



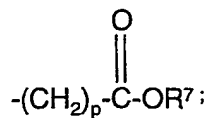
5

n is 0, 1, 2, 3 or 4;

y and z are independently 0 or 1;

* denotes the asymmetric carbon atom center;

R³ is hydrogen, lower alkyl or



10

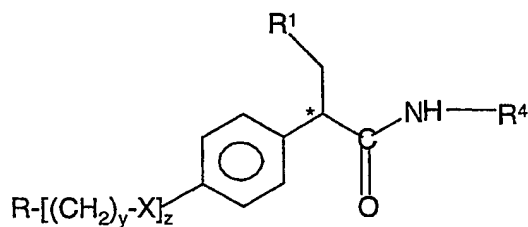
R⁶, R⁷ and R⁸ are independently hydrogen or lower alkyl; and

p is an integer from 0 to 5;

or a pharmaceutically acceptable salt thereof.

15

2. The amide of claim 1 wherein said compound is

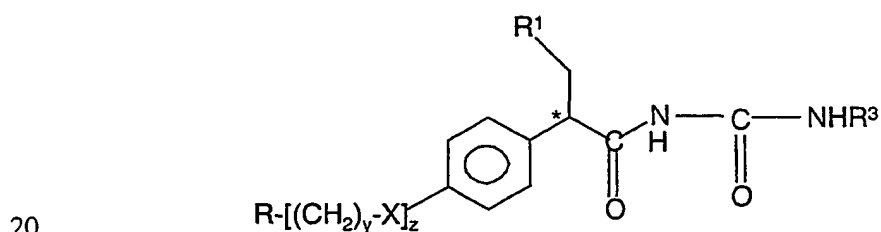


wherein *, y, z, X, R and R¹ are as defined in claim 1; and

R^4 is a five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amide group shown, which heteroaromatic ring contains from 1 to 3 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen with a first heteroatom being nitrogen which is adjacent to the connecting ring carbon atom, said heteroaromatic ring being unsubstituted or monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, $-(CH_2)_n-OR^6$, $-(CH_2)_n-C(O)OR^7$, or $-C(O)-C(O)OR^8$; and n , R^6 , R^7 and R^8 are as defined in claim 1.

- 10 3. The amide of claim 2 wherein R^4 is thiazolyl or pyridyl connected by a ring carbon atom to the amide group shown, with the nitrogen atom being adjacent to the connecting ring carbon atom, said thiazolyl or pyridyl being unsubstituted or monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, $-(CH_2)_n-OR^6$, $-(CH_2)_n-C(O)OR^7$, or $-C(O)-C(O)OR^8$; wherein n , R^6 , R^7 and R^8 are as defined in claim 1.

4. The amide of claim 1 wherein said compound is



wherein $*$, y , z , X , R , R^1 and R^3 are as defined in claim 1.

- 25 5. The amide of claim 2 wherein R^3 is hydrogen or lower alkyl.
6. The amide of any of claims 1 to 5 wherein R^1 is cyclopentyl.

7. The amide of any of claims 1 to 6 wherein R is phenyl or naphthyl.
8. The amide of any of claims 1 to 6 wherein R is a heteroaromatic ring, connected by a ring carbon atom, which contains from 5 to 6 ring members with from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur or nitrogen.
9. The amide of claim 8, wherein R is thienyl, pyridyl or imidazolyl.
10. The amide of any of claims 1 to 6 wherein R is phenyl or naphthyl fused with a heteroaromatic ring containing 5 or 6 ring members with 1 or 2 heteroatoms in the ring being selected from the group consisting of nitrogen, oxygen or sulfur.
11. The amide of claim 10, wherein R is indolyl.
12. The amide of any of claims 1 to 6 wherein R is a saturated 5- or 6-membered cycloheteroalkyl ring, which contains from 1 to 2 heteroatoms selected from the group consisting of oxygen, sulfur and nitrogen.
13. The amide of claim 12, wherein R is morpholino.
14. The amide of any of claims 1 to 6 wherein R is cyclopentyl or cyclohexyl.
15. The amide of any of claims 1 to 14 wherein X is $-\text{SO}_2-$.
16. The amide of any of claims 1 to 14 wherein X is $-\text{O}-$.
17. The amide of any of claims 1 to 16 wherein z is 0.
18. The amide of any of claims 1 to 16 wherein z is 1.
19. The amide of any of claims 1 to 18 wherein n is 0, 1 or 2.

20. The compound of any of claims 1 to 19 wherein X is -O- or -S(O)₂-; R is a heteroaromatic ring, connected by a ring carbon atom, which contains from 5 to 6 ring members with from 1 to 2 heteroatoms selected from sulfur or nitrogen, aryl containing 6 or 10 ring carbon atoms, aryl containing from 6 to 10 ring carbon atoms fused with a heteroaromatic ring containing 5 ring members with 1 nitrogen atom in the ring; or a saturated 6-membered cycloheteroalkyl ring, which contains 2 heteroatoms selected from oxygen and nitrogen; or a cycloalkyl ring having 5 or 6 carbon atoms; R¹ is a cycloalkyl ring having 5 carbon atoms; R² is -C(O)-NHR³, a five- or six-membered heteroaromatic ring connected by a ring carbon atom to the amide group shown, which heteroaromatic ring contains 1 or 2 heteroatoms selected from sulfur and nitrogen with a first heteroatom being nitrogen which is adjacent to the connecting ring carbon atom, said heteroaromatic ring being unsubstituted or monosubstituted at a position on a ring carbon atom other than adjacent to said connecting carbon atom with a substituent selected from the group consisting of lower alkyl, -(CH₂)_n-OR⁶, -(CH₂)_n-C(O)OR⁷, or -C(O)-C(O)OR⁸; n is 0, 1 or 2; y and z are independently 0 or 1, * denotes the asymmetric carbon atom center; R³ is hydrogen or lower alkyl; R⁶ is hydrogen; R⁷ is hydrogen or lower alkyl; and R⁸ is lower alkyl.

21. A compound of any of claims 1 to 20 selected from the group consisting of:

2-biphenyl-4-yl-3-cyclopentyl-N-thiazol-2-yl-propionamide,
 (2R)-2-biphenyl-4-yl-3-cyclopentyl-N-thiazol-2-yl-propionamide,
 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-N-thiazol-2-yl-propionamide,
 [2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazol-4-yl]-acetic acid methyl ester,
 [2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazol-4-yl]-acetic acid ethyl ester,
 2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazole-4-carboxylic acid ethyl ester,

- 2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazole-4-carboxylic acid methyl ester,
- {2-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid methyl ester,
- 5 {2-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-thiazol-4-yl}-acetic acid ethyl ester,
- 2-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-thiazole-4-carboxylic acid methyl ester,
- [2-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-thiazol-4-yl]-oxo-acetic acid
- 10 ethyl ester,
- 2-biphenyl-4-yl-3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-propionamide,
- 2-biphenyl-4-yl-3-cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-propionamide,
- 3-cyclopentyl-N-[4-(2-hydroxyethyl)-thiazol-2-yl]-2-(4-naphthalen-1-yl-phenyl)-propionamide,
- 15 3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-naphthalen-1-yl-phenyl)-propionamide,
- 2-biphenyl-4-yl-3-cyclopentyl-N-pyridin-2-yl-propionamide,
- 3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-N-pyridin-2-yl-propionamide,
- 6-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-nicotinic acid methyl ester,
- 20 6-(2-biphenyl-4-yl-3-cyclopentyl-propionylamino)-nicotinic acid,
- 2-biphenyl-4-yl-3-cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-propionamide,
- 6-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-nicotinic acid methyl ester,
- 6-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionylamino]-nicotinic acid,
- 25 3-cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-2-(4-naphthalen-1-yl-phenyl)-propionamide,
- 3-cyclopentyl-N-thiazol-2-yl-2-(4-thiophen-2-yl-phenyl)-propionamide,
- 3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-N-thiazol-2-yl-propionamide,
- 3-cyclopentyl-2-(4-pyridin-4-yl-phenyl)-N-thiazol-2-yl-propionamide,
- 30 3-cyclopentyl-N-pyridin-2-yl-2-(4-pyridin-4-yl-phenyl)-propionamide,
- 3-cyclopentyl-N-pyridin-2-yl-2-(4-pyridin-3-yl-phenyl)-propionamide,

- 3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-N-thiazol-2-yl-propionamide,
 3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-N-thiazol-2-yl-propionamide,
 2-(4-benzyloxy-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
 3-cyclopentyl-2-(4-phenoxy-phenyl)-N-thiazol-2-yl-propionamide,
 5 3-cyclopentyl-2-(4-phenoxy-phenyl)-N-pyridin-2-yl-propionamide,
 {2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic
 acid ethyl ester,
 3-cyclopentyl-N-(4-hydroxymethyl-thiazol-2-yl)-2-(4-phenoxy-phenyl)-
 propionamide,
 10 2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazole-4-carboxylic
 acid methyl ester,
 3-cyclopentyl-N-[4-(2-hydroxy-ethyl)-thiazol-2-yl]-2-(4-phenoxy-phenyl)-
 propionamide,
 {2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic
 15 acid,
 {2-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-thiazol-4-yl}-acetic
 acid methyl ester,
 3-cyclopentyl-N-(5-methyl-pyridin-2-yl)-2-(4-phenoxy-phenyl)-propionamide,
 6-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-nicotinic acid
 20 methylester,
 6-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionylamino]-nicotinic acid,
 3-cyclopentyl-N-(5-hydroxymethyl-pyridin-2-yl)-2-(4-phenoxy-phenyl)-
 propionamide,
 2-(4-benzenesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
 25 2-(4-cyclopentanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
 2-(4-cyclohexanesulfonyl-phenyl)-3-cyclopentyl-N-thiazol-2-yl-propionamide,
 3-cyclopentyl-2-[4-(1H-imidazole-2-sulfonyl)-phenyl]-N-thiazol-2-yl-
 propionamide,
 (2-biphenyl-4-yl-3-cyclopentyl-propionyl)-urea,
 30 1-(2-biphenyl-4-yl-3-cyclopentyl-propionyl)-3-methyl-urea,
 1-[3-cyclopentyl-2-(4-naphthalen-1-yl-phenyl)-propionyl]-3-methyl-urea,

1-[3-cyclopentyl-2-(4-pyridin-3-yl-phenyl)-propionyl]-3-methyl-urea,
1-{3-cyclopentyl-2-[4-(1H-indol-5-yl)-phenyl]-propionyl}-3-methyl-urea,
1-[3-cyclopentyl-2-(4-morpholin-4-yl-phenyl)-propionyl]-3-methyl-urea,
1-[2-(4-cyclohexanesulfonyl-phenyl)-3-cyclopentyl-propionyl]-3-methyl-urea,
5 and
1-[3-cyclopentyl-2-(4-phenoxy-phenyl)-propionyl]-3-methyl-urea.

22. A pharmaceutical composition comprising a compound of any of claims 1
to 21 and a pharmaceutically acceptable carrier and/or adjuvant.

23. A process for the preparation of a pharmaceutical composition of claim 22
comprising combining a compound of formula I according to any one of claims 1 to 21
with a pharmaceutically acceptable carrier and/or adjuvant.

24. The compounds according to any of claims 1 to 21 for use as a therapeutic
active substance.

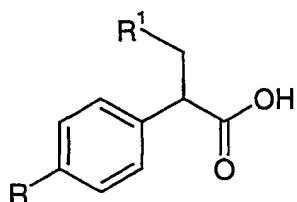
25. The use of the compounds according to any of claims 1 to 21 for the
treatment or prophylaxis of type II diabetes.

26. The use of a compound according to any of claims 1 to 21 for the
preparation of a medicament for the treatment or prophylaxis of type II diabetes.

27. A method for the prophylactic or therapeutic treatment of type II diabetes,
which method comprises administering a compound of any of claims 1 to 21 to a human
being or an animal.

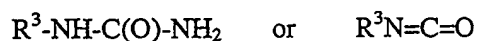
28. A process for the preparation of a compound of formula I according to
claim 1, which process comprises:

(a) reacting a compound of formula



wherein R and R¹ are as defined in claim 1;

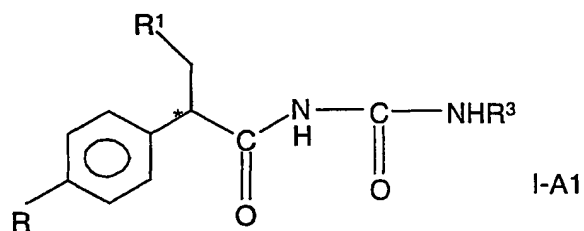
with a compound of the formula



5

wherein R³ is as defined in claim 1;

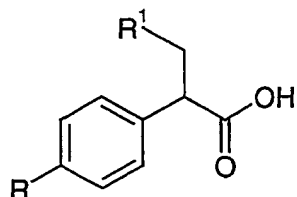
to a compound of the formula I-A1



wherein R, R¹ and R³ are as defined in claim 1; or

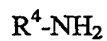
10

(b) reacting a compound of formula



wherein R and R¹ are as defined in claim 1;

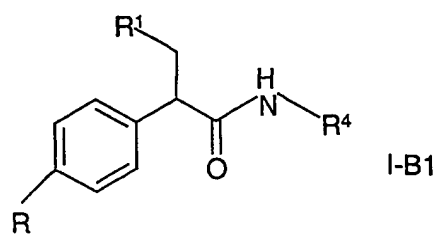
with a compound of the formula



15

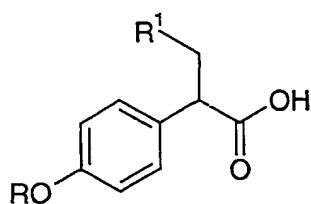
wherein R⁴ is as defined in claim 1;

to a compound of the formula I-B1



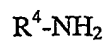
wherein R, R¹ and R⁴ are as defined in claim 1; or

(c) reacting a compound of formula



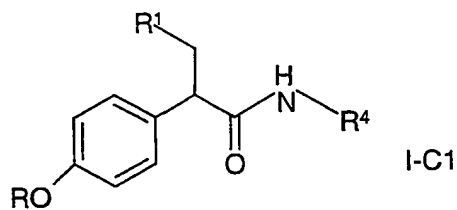
wherein R and R¹ are as defined in claim 1;

with a compound of the formula



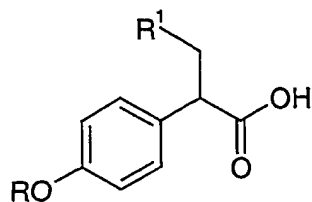
wherein R⁴ is as defined in claim 1;

to a compound of the formula I-C1



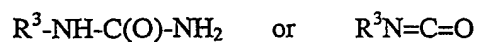
wherein R, R¹ and R⁴ are as defined in claim 1; or

(d) reacting a compound of formula



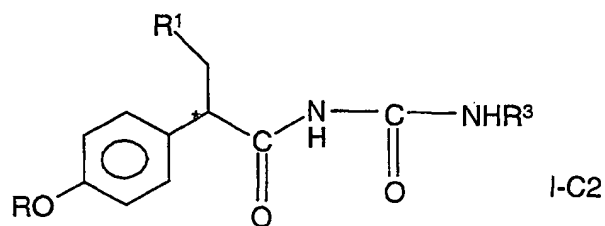
wherein R and R¹ are as defined in claim 1;

with a compound of the formula



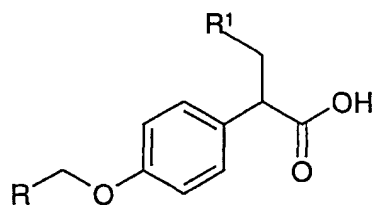
wherein R^3 is as defined in claim 1;

to a compound of the formula I-C2



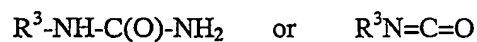
wherein R , R^1 and R^3 are as defined in claim 1; or

(e) reacting a compound of formula



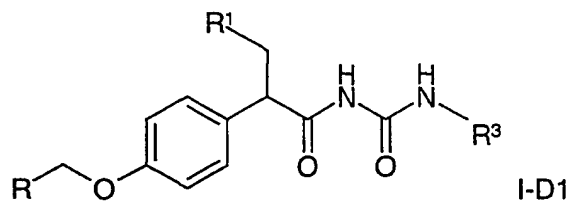
wherein R and R^1 are as defined in claim 1;

with a compound of the formula



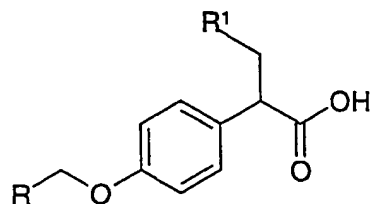
wherein R^3 is as defined in claim 1;

to a compound of the formula I-D1



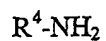
wherein R , R^1 and R^3 are as defined in claim 1; or

(f) reacting a compound of formula



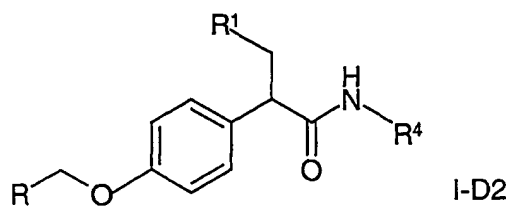
wherein R and R¹ are as defined in claim 1;

with a compound of the formula



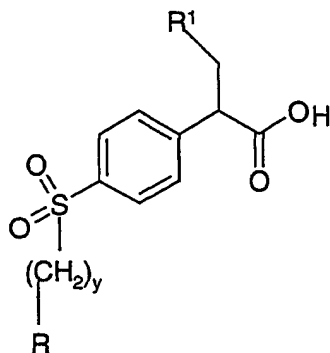
5 wherein R⁴ is as defined in claim 1;

to a compound of the formula I-D2



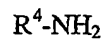
wherein R, R¹ and R⁴ are as defined in claim 1; or

10 (g) reacting a compound of formula



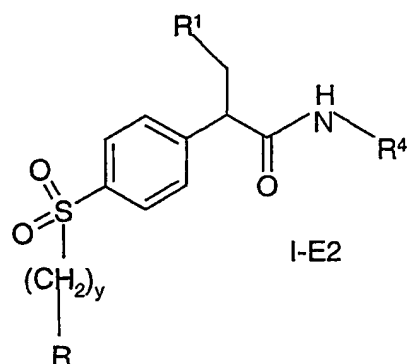
wherein y, R and R¹ are as defined in claim 1;

with a compound of the formula



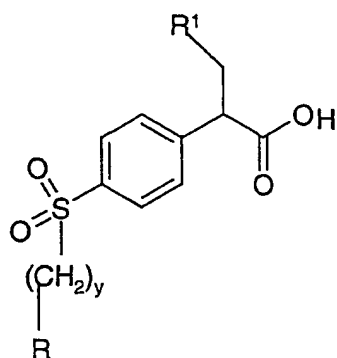
15 wherein R⁴ is as defined in claim 1;

to a compound of the formula I-E2



wherein y , R , R^1 and R^4 are as defined in claim 1; or

(h) reacting a compound of formula



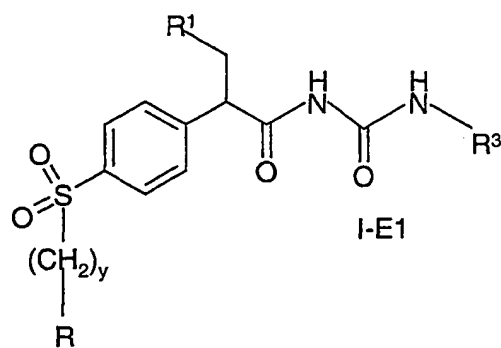
wherein y , R and R^1 are as defined in claim 1;

with a compound of the formula



wherein R^3 is as defined in claim 1;

to a compound of the formula I-E1



wherein y, R, R¹ and R³ are as defined in claim 1.

29. A compound prepared by any of the processes according to claim 28.
- 5 30. The invention as hereinbefore defined.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/04777

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7	C07D277/46	C07D277/56 C07D213/75 C07D213/80 C07D417/12 C07D213/56 C07D209/18 C07D295/155 C07C317/44 A61K31/426 A61K31/427 A61K31/44 A61K31/4427 A61K31/404 A61K31/17
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D C07C A61K A61P		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 776 917 A (MANN T A ET AL) 4 December 1973 (1973-12-04) the whole document	1,22-27
P,X	WO 00 58293 A (F. HOFFMANN-LA ROCHE AG) 5 October 2000 (2000-10-05) the whole document	1-29
<input type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *G* document member of the same patent family		
Date of the actual completion of the international search 28 August 2001		Date of mailing of the international search report 10/09/2001
Name and mailing address of the ISA European Patent Office, P.B. 5618 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Allard, M

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 30

The scope of claim 30 is so unclear (Article 6 PCT) that a meaningful International Search is impossible with regard to this claim.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/04777

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 3776917	A	04-12-1973	NONE	
WO 0058293	A	05-10-2000	AU 3963000 A	16-10-2000